Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 2018;378:439-48. DOI: 10.1056/NEJMoa1709866

17-09866 – CTL019 in Children and Young Adults with Leukemia (ELIANA)

This supplement contains the following items:

1. Final, redacted protocol, summary of changes.
2. Final, redacted statistical analysis plan, summary of changes.

NOVARTIS

Clinical Development

CTL019

Protocol CCTL019B2202

A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia

Authors [redacted]

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALC	Absolute Lymphocyte Count
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine Aminotransferase/Glutamic Pyruvic Transaminase/SGPT
AML	Acute Myeloid Leukemia
Anti-HBc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase/Glutamic Oxaloacetic Transaminase/SGOT
ATG	Anti-thymocyte globulin
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AUMC	Area under the first moment curve
B-ALL	B cell lineage acute lymphoblastic leukemia
4-1 BB	type 2 transmembrane glycoprotein belonging to the TNF superfamily, expressed on activated T Lymphocytes
BCR-ABL	Philadelphia Chromosome
BiPAP	Bilateral Positive Airway Pressure
BM	Bone Marrow
BMT	Bone Marrow Transplantation
BOR	Best Overall Response
BUN	Blood Urea Nitrogen
CAR	Chimeric Antigen Receptor
CBC	Complete Blood Count
CCGs	CRF Completion Guidelines
CD	Cluster of Differentiation
CD137	4-1BB costimulatory molecule
CFR	Code of Federal Regulations
CHP	Children's Hospital of Philadelphia
CI	Confidence Interval
CIF	Cumulative Incidence Function
CLL	Chronic Lymphocytic Leukemia
C_{max}	Maximum concentration
CMV	Cytomegalovirus
CNS	Central Nervous System
CPAP	Continuous Positive Airway Pressure
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CR	Complete remission
CRi	Complete remission with incomplete blood count recovery
CRO	Contract Research Organization
CR_p	Complete remission with incomplete platelet recovery
CRP	C-Reactive Protein
CRS	Cytokine Release Syndrome
CSF	Cerebral Spinal Fluid

[redacted]

CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T Lymphocyte
CTL019 cells	CD 19 redirected autologous T cells (also called CART19 cells)
CVPF	Cell and Vaccine Production Facility
DOR	Duration of Remission
DLBCL	Diffuse Large B Cell Lymphoma
DLI	Donor Lymphocyte Infusion
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DS&E	Novartis Drug Safety and Epidemiology Department
EBV	Epstein-Barr Virus
EC	European Commission
ECG	Electrocardiogram
ECHO	Echocardiogram
EDC	Electronic Data Capture
EFS	Event Free Survival
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment and Primary Follow-Up
EQ-5D	European Quality of Life 5 Dimensions
FAB	French-American-British
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFP	Fresh Frozen Plasma
FISH	Fluorescent *in situ* hybridization
FL	Follicular Lymphoma
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factor
GMP	Good Manufacturing Practice
GU	Genitourinary
GVHD	Graft versus Host Disease
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLT	High level term
IB	Investigator Brochure
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
Ig	Immunoglobulin

[redacted]

IL	Interleukin
IL6R	Interleukin 6 receptor
IN	Investigator Notification
INR	International Normalized Ratio
IRC	Independent Review Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISBT	International Society of Blood Transfusion
IUD	Intrauterine Device
i.v.	Intravenous(ly)
IVIG	Intravenous Immunoglobulin
KM	Kaplan Meier
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLOQ	Lower Limit of Quantification
LOQ	Limit of Quantification
LP	Lumbar Puncture
LPLV	Last Patient Last Visit
LVEF	Left Ventricular Ejection Fraction
LVSF	Left Ventricular Shortening Fraction
MAP	Master Analysis Plan
MAS	Macrophage Activation Syndrome
MCHC	Mean Corpuscular Hemoglobin Concentration
MCL	Mantle Cell Lymphoma
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Authorities
MHC	Major Histocompatibility Complex
MLL	Mixed-Lineage Leukemia
MNC	Mononuclear Cells
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MRT	Mean Residence Time
MUGA	Multiple Uptake Gated Acquisition
MYC	A regulator gene located on chromosome 8 that is disregulated via translocations in Burkitt's lymphoma/leukemia
NCCN	National Comprehensive Cancer Network
NE	Norepinephrine Equivalent
NHL	non-Hodgkin’s lymphomas
NR	No Response
O_2	Oxygen
ORR	Overall Remission Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PE	Physical examination
PedsQL	Pediatric Quality of Life questionnaire

[redacted]

PGS-CRS	The Penn Grading Scale for Cytokine Release Syndrome
pH	Hydrogen ion concentration; a measure of the acidity or basicity of an aqueous solution
Ph+	Philadelphia Chromosome Positive
PHI	Personal Health Information
PI	Principal Investigator
PK	Pharmacokinetics
PML	Progressive Multifocal Leukoencephalopathy
PPS	Per-Protocol Set
PR	Partial Remission
PRO	Patient Reported Outcomes
PT	Preferred Term
PT	Prothrombin Time
q-PCR	Quantitative Polymerase Chain Reaction
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RCL	Replication Competent Lentivirus
RDC	Remote Data Capture
REB	Research Ethics Board
RFS	Relapse Free Survival
r/r	Relapsed or refractory
SAE	Serious Adverse Event
SC	Steering Committee
scFv	Single chain Fv fragment of an antibody
SCID	Severe Combined Immunodeficiency
SCT	Stem Cell Transplantation
sIg	Surface Immunoglobulin
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Event
TKI	Tyrosine Kinase Inhibitor
T_{max}	Time to peak concentration
TNF	Tumor Necrosis Factor
TLS	Tumor Lysis Syndrome
TCR	T Cell Receptor
TCR-zeta	Signaling domain found in the intracellular region of the TCR zeta, gamma and epsilon chains
ULN	Upper Limit of Normal
UPCC	University of Pennsylvania Cancer Center
VASST	Vasopressin and Septic Shock Trial
V_H	Heavy Chain Variable Domain
V_L	Light Chain Variable Domain
VSV-G	Vesicular Stomatitis Virus, Glycoprotein
WBC	White Blood Cell

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; defined as the point at which a patient meets all inclusion/exclusion criteria, and after which the patient's apheresed product is received and accepted by the Novartis designated manufacturing facility.
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US Code of Federal Regulations (CFR) 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number	A unique identifying number assigned to each patient who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient as part of the required study procedures, including active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Supportive treatment	Refers to any treatment required by the exposure to a study treatment
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

[redacted]

Amendment 4 (14-Jun-2016)

Amendment rationale

At the time of this protocol amendment, 26 sites have been initiated, 76 patients have been enrolled globally, and 54 patients have been infused with CTL019 manufactured in the US.

In published data (Grupp 2013, Grupp 2014, Maude 2015) with CTL019 and in current clinical trial experience, all complete remissions in pediatric ALL have been achieved no later than Month 3 post-CTL019 infusion. Discussions with the FDA have indicated that a 3 month follow-up may be adequate for initial submission to the FDA to support the marketing authorization of CTL019 in the US.

Therefore, the post-infusion follow-up duration for assessing the primary objective of ORR for each patient has been changed from 6 months to 3 months. Patients will continue to be follow-up for efficacy assessments according to Amendment 3 (No change in this regard in Amendment 4).

Novartis plans to use the CTL019 manufacturing process at the [redacted] Germany, a CMO to establish a second manufacturing site. Therefore, an additional cohort of patients (up to 14) will be enrolled from the EU to treat them with CTL019 manufactured at the facility in Europe ([redacted]) has been included to assess the efficacy, safety and in vivo cellular pharmacokinetics of patients infused with CTL019 manufactured by [redacted], and to assess clinical product comparability between the US and EU manufacturing facilities. To support the analysis, an additional secondary endpoint has been introduced. Therefore, the approximate total number of enrolled patients has been revised to 95 patients.

Two additional key secondary endpoints have been incorporated to allow evaluation of ORR and MRD-negative ORR only for CTL019 manufactured at the US manufacturing facility.

An interim analysis has been planned to be conducted with the first 50 CTL019 infused patients after they have either completed 3 months of follow-up or discontinued earlier.

The schedule of immunogenicity collections has been reduced and limited to 12 months post-CTL019 infusion. This reduced collection is based upon a single CTL019 infusion schedule versus chronic study treatment dosing where in the former an extended sample collection is not informative due to the lack of repeated dosing.

A minimum of one year follow-up at the treating investigational site is strongly recommended with remote follow-up as a possibility beyond this one year periods for the following reasons:

- Relapse patterns and kinetics of relapsed/refractory pediatric ALL patients (majority of relapses following CTL019 occur within one year)
- Relapse and survival in this population can be adequately collected by the referring pediatric oncologist
- Treatment schedule is a single dose infusion with limited incentive to return to a treatment site
- Alignment with FDA

[redacted]

A subgroup analysis has been added for patients with Down Syndrome given their known increased treatment related ALL morbidity and mortality rates. Because of increased risk, stem cell transplant is often not recommended in this population. Therefore, the experience with CTL019 in this rare population may address this unmet medical need.

The modified data capture for concomitant medications has been clarified to ensure data capture of blood products related to a reportable AE or SAE which assists analysis of the overall CTL019 safety profile.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/EC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Changes to Protocol

1. Section 2.2: Sample size updated.
2. Table 3-1: Updated primary, key secondary, and other secondary objectives/endpoints
3. Section 4.1: Updated with additional enrollment for manufacturing from [redacted]
4. Section 5.1: Sample size updated to include patients manufactured from [redacted]
5. Section 6.1.1.1: Section updated with clarifications
6. Table 6-1: Penn grading scale for CRS Grade 3 updated to include fibrinogen concentrate
7. Table 7-1: Updated with clarifications and revision to immunogenicity collections
8. Table 7-2: Updated with clarifications and addition of immunogenicity collections
9. Section 7.1.3: Updated visit assessments based on Table 7-1
10. Section 7.1.3.2: Section updated to include importance of return to investigational site within first year post-infusion
11. Section 7.1.4: Section updated with clarifications
12. Section 7.1.5: Section updated with clarifications
13. Table 7-5: Correction of errors
14. Section 7.2.3: Tables updated to include unscheduled collection at relapse
15. Tables 7-13 and Table 7-14: Updated immunogenicity sample collection schedule per Table 7-1 and Table 7-2
16. Table 7-15 and Table 7-16: Updated to include collection plan for additional doses of tocilizumab and siltuximab

[redacted]

17. Table 7-17: Updated to include unscheduled collection at relapse
18. Section 7.2.5: Section updated.
19. Section 10: Entire section updated to capture analysis plans for updated/new protocol objectives at interim and primary analysis, addition of down syndrome subgroup, and better define prior response status at baseline
20. Table 10-3: Clarification on AESI group team
21. Appendix 3: Updated to include clarification on blood product reporting in pre-treatment and treatment period

[redacted]

Amendment 3 (13-Apr-2016)

Amendment rationale

At the time of this protocol amendment, 26 sites have been initiated, 69 patients have been enrolled, and 41 patients have been infused with CTL019.

The protocol is being amended to institute updates on safety, manufacturing of CTL019 product, patient management, and eligibility criteria based on experiences from ongoing trials and recommendations from Health Authorities, Study Steering Committee and Data Monitoring Committee.

Key changes include:

1. Clinical experience (Section 1.2.1.2) updated to include more recent data and outcome of first 3 patient run-in data from this trial.
2. Target CTL019 dose range for patients > 50 kg has been expanded, and allowable infused dose ranges have been defined.

   The allowable infused cell dose range of CTL019 transduced cells have been defined as 0.2 to 5.0 x 10^6 autologous CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 0.1 to 2.5 x 10^8 autologous CTL019 transduced viable T cells (for patients > 50 kg) based on updated manufacturing cell dose release criteria. CTL019 products below these minimum transduced cell doses will not be released for infusion.

   The target cell dose range for purposes of trial analysis remains unchanged for patients ≤ 50 kg and for patients > 50 kg a range has also now been specified (1 to 2.5 x 10^8 transduced CTL019 cells

   The statistical plan for the per protocol dose analysis for 2 to 5 x 10^6 CTL019 transduced viable T cells per kg body weight is unchanged, and the 1 to 2.5 x 10^8 CTL019 transduced viable T cells is now provided as a range. At the time of this amendment, no patient has received a dose < 0.2 x 10^6 CTL019 transduced viable T cells. This change is considered to have a minimal impact on the per protocol dose statistical analysis.
3. Method of bone marrow MRD analysis in the key secondary endpoint was changed from qPCR to flow cytometry due to suboptimal sensitivity of the qPCR assay. Analysis by qPCR will be an exploratory endpoint.
4. Cellular immunogenicity analysis will be changed to an exploratory endpoint because the assay is not fully validated.
5. Cell counts for leukapheresis collection have further been clarified to better inform investigators and optimize collection for manufacturing, in addition to the collection of sentinel vials to better characterize apheresis product at the manufacturing site.
6. Extended the allowance of more than 10 patients ≥ 18 years old after Sponsor approval
7. ECHO/MUGA screening assessment may be performed within 7 days of screening.
8. IUD in place prior to consent may remain in place.

[redacted]

9. Medication restrictions updated. Use of steroids for non-GVHD and GVHD indications has been further clarified. Time windows have been revised to accommodate the respective medication half-lives and dose, and expected time to toxicity resolution (i.e. prior radiotherapy).
    - Clarification that systemic steroids have 72 hour restriction for non-GVHD indications
    - Systemic steroids added to GVHD therapy restrictions
    - Tyrosine kinase inhibitors and hydroxyurea must be stopped > 72 hours prior to CTL019 infusion
    - Hydroxyurea removed from restriction within 1 week prior to CTL019 infusion as this has been changed to 72 hours for this medication
    - Methotrexate $\geq$ 25 mg/m^2 added to 2 week chemotherapy restriction
    - Non-CNS and CNS radiotherapy added with time windows
    - Anti T-cell antibodies prohibited within 8 weeks prior to CTL019 infusion
10. Due to the continued experience with CTL019 in over 100 patients with pediatric r/r ALL, the study no longer requires pausing the study for certain life threatening events and deaths suspected to be related to CTL019 therapy.
11. CRS algorithm and management updated with additional details to support trial investigators on appropriate CRS management.
    - Included recommended time intervals between subsequent doses of steroids and anti-cytokine therapies based on cumulative experience in 3 pediatric r/r ALL trials.
    - Added siltuximab within the CRS algorithm to be given following the 2nd dose of tocilizumab due to encouraging experience to date with this anti-cytokine therapy in pediatric and adult ALL patients.
    - Recommended that TNF antagonists not be used for CTL019 associated CRS because lack of activity seen to date and the concerns about their immunosuppressive effects.
12. Secondary follow-up phase revised to allow for remote visits and abbreviated AE/concomitant medication collection in order to maximize patient data collection post CTL019 infusion in non-responding patients and in patients undergoing further anti-tumor therapy to meet health authority requirements on cell and gene therapy trials.
13. AESI profile updated based on most current CTL019 safety profile
14. Pediatric ALL efficacy guidelines have been updated to further address certain areas of ambiguity for response assessments involving bone marrow biopsy or aspirate, peripheral blood, and timing of baseline assessments.
    - Trilineage Hematopoiesis (TLH) was removed as one of the components of CR definition in the bone marrow: ALL NCCN criteria do list this as a recommended bone marrow component for response. However, exact criteria for bone marrow TLH are not well established and potentially poorly reproducible. This can alternately be supported, in a reproducible and quantitative manner, by the use of peripheral blood platelet and neutrophil minimum values in the absence of transfusion of these blood components.

[redacted]

- Changes and rationale of other tumor response elements are listed in Appendix 14.1 document history.

15. Exploratory objective is to correlate the relationship between CRS and clinical tumor response. Since CRS typically occurs by Day 28 and all tumor responses noted to date occurred by Day 28, it is justified to use the same time point for these two correlates.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/EC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Changes to Protocol

1. Section 1.2.1: Correction of typographical error
2. Section 1.2.1.2: Updated with more recent data.
3. Table 1-1: Table removed and reader directed to most current Investigator Brochure
4. Section 2.2: Enrollment numbers corrected.
5. Section 2.3: Target dose updated for patients > 50 kg updated
6. Section 2.3.1: Section added to include allowable infused cell dose range
7. Section 2.6: Added to include short description of risks and benefits
8. Table 3-1: Update to key secondary, other secondary, and exploratory endpoints.
9. Section 4.1.1: Section updated to include ALC and CD3 counts for leukapheresis collection and requirement for sample sentinel vials
10. Section 5.1: Updated to include clarity on patients ≥ 18 years of age
11. Section 5.2: Added window within screening for ECHO/MUGA assessments
12. Section 5.3: Updated contraception and concomitant medication criteria.
13. Section 6.1: Updated with new target and allowable infused cell dose ranges
14. Section 6.1.1.1: Clarification regarding use of alternative LD chemo regimen
15. Section 6.1.1.2: Updated to require influenza treatment be administered per label, updated concomitant medication restrictions, and added requirement of siltuximab on site within 24 hours of infusion per new CRS algorithm
16. Section 6.1.3: Title updated and clarifications added regarding CRS management
17. Section 6.2.3.3: Section removed
18. Section 6.2.4.1: Clarifications added
19. Section 6.2.4.2: CRS section updated to include details around cardiac monitoring, coagulopathy, and neurotoxicity
20. Figure 6-1: CRS management algorithm updated for more optimal CRS management
21. Figure 6-2: Figure removed

[redacted]

22. Section 6.2.4.3: Hepatitis B reactivation updated and new or secondary malignances toxicity added
23. Section 6.2.6: Added reference to Appendix 3: CTL019 Modified Data Reporting
24. Section 6.2.7: Updated prohibited concomitant medication criteria
25. Section 6.3: Added section and relevant sub-sections to include liver safety monitoring details
26. Section 6.4.1: Clarifications added
27. Section 6.5: Clarifications added
28. Section 6.5.1: Updated with new CTL019 dose ranges
29. Section 6.5.2: Minor updates added
30. Section 6.5.3.1: Clarification added
31. Table 7-1: Primary follow-up visit evaluation schedule updated
32. Table 7-2: Secondary follow-up visit evaluation schedule updated
33. Section 7.1.1: Section updated
34. Section 7.1.1.2: Title and section updated
35. Section 7.1.2: Section updated
36. Section 7.1.3: Section updated
37. Section 7.1.4: Section updated to include new secondary follow-up assessment schedule and details. AE and concomitant medication reporting details added
38. Section 7.2.2.4: Section updated to clarify tanner staging only for patients < 18 years old
39. Section 7.2.2.5: Section updated
40. Table 7-5: Local laboratory collections updated
41. Table 7-6: Central laboratory collections updated
42. Table 7-12: Table added to account for CTL019 transgene persistence during secondary follow-up phase
43. Section 7.2.4: Clarifications added
44. Section 7.2.5: New section added
45. Section 7.2.7.3: Clarifications added regarding translations and completion of questionnaires
46. Section 8.1.2: Section updated
47. Section 8.2.2: Section updated
48. Section 8.4: Section updated with new contraception and pregnancy language
49. Section 9.3: Updated to include manufacturing facility data entry
50. Section 9.4: Updated to include manufacturing facility data
51. Section 10.1.5: Section updated
52. Section 10.2: Section updated
53. Table 10-1: Updated according to efficacy guideline revisions
54. Section 10.4.4.1: Section updated
55. Section 10.5.1.1: Section updated
56. Section 10.5.2.3: Section updated

[redacted]

57. Section 10.5.2.10: Section updated
58. Section 10.5.3.2: AESI updates
59. Section 10.5.3.4: Section updated
60. Table 10-3: AESI terms updated
61. Section 10.5.3.7: Section updated
62. Section 10.5.3.9: Section updated
63. Table 10-4: PK parameters updated
64. Section 11.7: Clarification on confidentiality added
65. Section 13: References updated
66. Section 14.1: Appendix 1 updated with newest efficacy evaluation guidelines
67. Section 14.3: Appendix 3 added
68. Section 14.4: Appendix 4 added

[redacted]

Amendment 2

Amendment rationale

At the time of this protocol amendment, 1 site has been initiated, 3 patients have been enrolled, and 1 patient has been treated.

The protocol is being amended to ensure full alignment with the agreed binding measures detailed in the Pediatric Investigation Plan (PIP) opinion of the Paediatric Committee of the European Medicines Agency, issued on 20 March 2015 and to address recommendations from EMA Scientific Advice letter on 25 April 2014.

Key changes include:

1. The full analysis set should include at least 50 patients < 18 years (of which 10 patients are < 10 years old). The total number of enrolled patients has been increased accordingly to approximately 78 patients to be enrolled.
2. Elevation from secondary to key secondary endpoint for MRD by PCR based on its relevance as a surrogate marker correlated with clinical benefit in pediatric ALL. The sample size outlined above will provide 85 % to 91 % power to reject null hypothesis that percentage of patients with BOR of CR or CRi and MRD negative bone marrow <15% depending on the actual total number of patients infused with CTL019.
3. Elevation from exploratory endpoints to secondary endpoints relating to CRS, safety monitoring, and PROs
4. Addition of secondary objective: Derivation of a score to predict cytokine release syndrome
5. Day 28 tumor assessment window changed from +/- 7 days to +/- 4 days
6. Additional analyses have been included to assess the response at Day 28 +/- 4 days, impact of baseline tumor burden on response, etc.

In addition, other changes have been instituted for purposes of safety, clarity and feasibility based on experiences from ongoing trials as outlined below. Key changes include:

1. Clarifications to more accurately define the term “refractory ALL” in inclusion criteria #1. The two refractory populations now defined have equally poor prognosis at study enrollment and are not expected to negatively impact the population homogeneity.
2. Clarifications on influenza testing based on regions and seasonal variations
3. Extension of healthcare resource utilization collection visits
4. Clarifications on safety reporting and apheresis collections
5. Removal of PedsQL questionnaire collection in children ages 5-7

Changes to Protocol

1. Section 1.1: Correction of typographical errors
2. Section 1.2.1: Reference added
3. Table 1-1: Clarity added for patient population on the trials
4. Section 1.2.1.2: Clarification on correlation between administration of tocilizumab and CTL019 cell expansion

[redacted]

5. Section 2.1: References added
6. Section 2.3: Added “viable T” to dose
7. Table 3-1: Objectives and endpoints updated to include key secondary objective, addition of other secondary objectives, as well as shifting of exploratory objectives to secondary objectives.
8. Section 4.1.1: Clarity on guidelines for optimal apheresis collection
9. Section 4.1.1: Clarity on use of CTL019 manufactured cells if GVHD experienced after collection of apheresis product
10. Section 5.1: Patient population increased to approximately 78 patients enrolled, at least 50 infused patients < 18 years (at least 10 of which < 10 years)
11. Section 5.2: Clarification on the definition of refractory ALL added to criteria # 1
12. Section 5.3: Criteria # 10 retired and replaced with criteria # 15 with additional Anti T-cell therapy guidance
13. Section 6.1.1.2: Clarifications on influenza testing based on regions and seasonal variations. Anti T-cell Therapy details added. The number of tocilizumab doses required on site prior to CTL019 infusion changed to two doses. Clarification on which specific manual referenced. Guidance on monitoring of patient temperature added.
14. Section 6.1.3: Number of tocilizumab doses required on site prior to CTL019 infusion changed to two doses.
15. Section 6.2.4.2: CRS management algorithm to be followed by investigators
16. Section 6.2.6: Modified concomitant medication reporting better defined; clarification on concomitant medication recording prior to screening
17. Section 6.2.7: Anti T-cell Therapy guidance added
18. Section 6.4: Clarification on which specific manual referenced, and changed “the person” to “personnel” to ensure alignment with manuals
19. Section 6.4.2: Clarification on which specific manual referenced
20. Section 6.4.3: Clarification on which specific manuals referenced
21. Section 6.4.3.2: Clarification on which specific manual referenced
22. Section 6.4.4: Clarification on which specific manuals referenced
23. Table 7-1: Day 28 window changed from +/- 7 days to +/- 4 days
24. Table 7-1: Hospitalization status collection changed from Day 1 to screening
25. Table 7-1: MRD assessment by bone marrow aspirate by flow cytometry to include T cell counts
26. Table 7-1: MRD assessment in bone marrow aspirate by qPCR added for clarity
27. Table 7-1: “Aspirate” added to lymph node or other involved tissue assessment
28. Table 7-1: If bone marrow unavailable for genomic analysis, peripheral blood can be used if tumor cells are present in the peripheral blood at relapse
29. Section 7.1.1: “at the time of screening” added to performance status assessment; T cell numbers added to bone marrow aspirate and biopsy and peripheral blood flow cytometry
30. Section 7.1.2: Collection time point of PROs clarified at enrollment; Clarification on influenza testing based on regions and seasonal variations

[redacted]

31. Section 7.1.3: T cells added for flow cytometry; Day 28 window changed to +- 4 days; “aspirate” added to lymph node assessment
32. Section 7.1.3.3: If bone marrow aspirate is not available, peripheral blood can be used if tumor cells are present in the peripheral blood at relapse
33. Section 7.1.4: T cells added for flow cytometry
34. Table 7-3: T cells added for flow cytometry of peripheral blood
35. Section 7.2.2: Further Tanner staging not required if patient classified as Tanner stage 5
36. Section 7.2.2.4.1: Male tanner stage 5 (pubic hair) corrected
37. Table 7-5: CD4 and CD8 added to T cell levels
38. Table 7-6: CD4 and CD8 added to T cell levels
39. Section 7.2.3: Day 28 window changed to +/- 4 days for all applicable tables
40. Table 7-16: Day 28 window changed to +/- 4 days
41. Section 7.2.5: Hospitalization status collection changed from Day 1 to screening
42. Section 7.2.6: Collection time point of PROs clarified at enrollment; instruction that child should face away from the parent removed
43. Section 7.2.6.1: Removal of PedsQL Young Child for ages 5-7
44. Section 7.2.6.2: Clarifications and corrections made, and reference to PRO administration guidelines added
45. Section 8.1.2: Clarification added on adverse event reporting while patient simultaneously enrolled on CTL019B2206
46. Section 8.2.2: Clarification added on serious adverse event reporting while patient simultaneously enrolled on CTL019B2206
47. Section 8.4: “salpingotomy” corrected to “bilateral salpingectomy”
48. Section 10: Section updated with new population details
49. Section 10.1: Section updated based on new population
50. Section 10.2: Primary refractory definition clarified
51. Section 10.4 and subsections: Statistical analysis updates based on changes implemented in protocol
52. Section 10.5.1.1: Section updated
53. Section 10.5.2.2: Section updated
54. Section 10.5.2.4: Section removed (CR or CRi with MRD negative bone marrow)
55. Section 10.5.2.7: Section added
56. Section 10.5.2.8: Section added
57. Section 10.5.2.9: Section added
58. Section 10.5.2.10: Section added
59. Section 10.5.3.5: Section added
60. Section 10.5.3.6: Section added
61. Section 10.5.3.7: Section added
62. Section 10.5.3.9: Section updated
63. Section 10.5.4: Section update
64. Table 10-4: Table updated with more details

[redacted]

65. Section 10.6.1: Section updated
66. Section 10.6.1.3: Section updated
67. Section 10.6.4: Patient reported outcome section removed and moved to Section 10.5.2.7
68. Section 10.8: Section updated
69. Section 10.9: Section updated to include key secondary endpoint analysis
70. Section 13: References added

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/EC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

Amendment 1

Amendment rationale

At the time of this protocol amendment, no sites have been initiated and first patient first visit (FPFV) has not occurred. All sites are to be initiated with the current protocol amendment.

The protocol is being amended in order to include additional safety information and includes Health Authority feedback regarding reporting of SAEs including CRS and deaths, follow-up time required after a live birth, and revision of the inclusion criteria regarding the age at screening and local leukapheresis criteria.

Patient Report Outcomes (PROs) have been added to assess the patient's health related quality of life and patient function following cellular therapy.

The window between informed consent and CTL019 infusion has been widened from 8 weeks to 16 weeks. From ongoing phase I clinical trial experience in over 40 patients with r/r pediatric ALL receiving CTL019 therapy, the interval from ICF to CTL019 infusion has been up to 19 weeks. Pediatric patients exceeding a 12 week interval from ICF to infusion in this ongoing phase I trial have shown similar outcomes with CTL019 with no additional safety concerns compared to those patients with a time window less than 12 weeks. This widened time interval from 8 to 16 weeks is necessary to complete all of the following: patient screening, ongoing stabilization of r/r leukemic disease with salvage chemotherapy and the management of typical complications resulting from salvage chemotherapy and/or the prolonged cytopenias related to the disease itself (e.g. infections requiring hospitalization), manufacturing of the cell therapy product and administration of the LD chemotherapy. Apheresis could potentially also occur during this interval.

Additional PK and cytokine sample time points were added to better define cell expansion and CRS, as well as the addition of exploratory endpoints that did not impact total sample collection requirements.

Unnecessary testing of CMV and EBV at screening as per current guidelines for autologous blood product therapy has been removed.

In addition, other changes have been instituted for purposes of safety, clarity and feasibility based on experiences from ongoing trials as outlined below.

Changes to the protocol

1. Section 1.2.1.2: Updated clinical experience section with currently available data.
2. Table 1-2: Removed and replaced with summary text
3. Table 2-1: Removed and replaced with summary text
4. Table 3-1: Updated secondary endpoints and added exploratory endpoints.
5. Figure 4-1: Study design diagram updated with extended windows from ICF to CTL019 infusion.
6. Section 4.1.1: Clarifications around apheresis product and exploratory endpoint language added.

[redacted]

7. Section 5.2: Changed age at screening from age 2 at initial diagnosis to age 3 at screening. Added an additional inclusion criteria to confirm patient meets local institutional criteria for leukapheresis.
8. Section 5.3: Clarifications to testing time windows and chemotherapy in exclusion criteria.
9. Section 6.1.1.1: Clarification on timing of lymphodepleting chemotherapy before CTL019 infusion.
10. Section 6.1.1.2: Clarifications on patient safety and requirements prior to CTL019 infusion. Vital signs follow-up post CTL019 infusion updated in line with data from ongoing trials.
11. Section 6.1.3: Clarifications on recording of rescue medications in the clinical database.
12. Figure 6-1: CRF Management Algorithm updated based on experiences from ongoing trials.
13. Table 6-2: Adjustment of vasopressor doses corrected by weight
14. Sections 6.2.4.2 & 6.2.4.3: Safety information added based on most current IB.
15. Section 6.2.6: Clarification on administration of granulocyte colony stimulating factor (G-CSF).
16. Section 6.2.7: Clarifications added.
17. Section 6.3.1: Re-screening language removed and better delineation of pre-infusion requirements have been included
18. Table 7-1: Primary Follow-up VES updated with new time points, clarifications, updated windows, addition and removal of assessments, and updates to table references.
19. Table 7-2: Secondary Follow-up VES updated with clarifications and additional assessments.
20. Section 7.1.1: Clarifications made throughout section impacting patient safety.
21. Section 7.1.1.1: Removed section due to widened window between ICF and CTL019 infusion. Screening procedures requiring repeat have been incorporated into other sections of the protocol.
22. Section 7.1.1.2: Reference to an enrollment form has been removed. Error in previous version.
23. Section 7.1.2: Section updated with new visit windows and clarifications for patient safety.
24. Section 7.1.3: Section updated with new visit windows and clarifications for patient safety.
25. Section 7.1.3.3: Section updated for clarification.
26. Section 7.1.4: Section updated for clarification.
27. Section 7.1.4.1: Section updated for clarification on research results and biological samples.
28. Table 7-3: Table updated for clarification.
29. Section 7.2.2.4: Tanner staging guidelines for male genitalia and public hair stages and female breast stages and public hair stages added for clarity.
30. Section 7.2.5: Added resource utilization to capture hospitalizations
31. Section 7.2.6: Added patient reported outcomes
32. Table 7-5: Table updated for clarification.
33. Table 7-6: Table updated for clarification

[redacted]

34. Tables 7-7, 7-8, 7-9, 7-10, 7-11, 7-12, 7-13, 7-14, and 7-15: Tables updated for clarification of windows and sample requirements.
35. Section 7.2.3.1: Section updated for clarification.
36. Section 7.2.4: Section updated for clarification.
37. Table 7-16: Table updated for clarification of windows and sample requirements.
38. Section 7.2.6: Section updated to add PRO details.
39. Section 8.2.2: Section updated to address FDA requirements for CRS and deaths.
40. Section 8.4: Section updates to address FDA requirements for follow-up after live birth
41. Section 10.5.4: Section updated for clarification.
42. Section 10.6.1: Section updated for clarification.
43. Section 10.6.1.3: Section updated for clarification.
44. Section 10.6.4: Section added for patient reported outcomes
45. Section 10.6.5: Section added for healthcare resource utilization
46. Section 13: New references added.
47. Section 14.1.2.3.5: Revision to ALL response guidelines

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/EC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

Protocol summary:

Protocol number	CCTL019B2202
Title	A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed or refractory B-cell acute lymphoblastic leukemia
Brief title	Study of efficacy and safety of CTL019 in pediatric ALL patients
Sponsor and Clinical Phase	Novartis Phase II Multicenter
Investigation type	Biological
Study type	Interventional
Purpose and rationale	Outcome remains poor for patients with relapsed or refractory (r/r) pediatric B-cell lineage acute lymphoblastic leukemia (B-cell ALL). Treatment options for r/r B-cell ALL include further treatment with salvage chemotherapy, second allogeneic stem cell transplantation (SCT) or supportive care. Therapy in this population is not curative with an overall survival of 3 to 6 months. CD19 has emerged as an attractive therapeutic target because it is widely expressed on normal and malignant B-cells throughout B-cell maturation but not on pluripotent stem cells or non–B-cell tissues. The development of chimeric antigen receptor (CAR) T cells to target CD19+ cells (CART19 or CTL019) provides an innovative new approach to these malignancies. This approach involves autologous patient-derived T cells that are genetically modified *ex vivo* via lentiviral transduction to express a CD19 antigen recognition domain attached to intracellular signaling domains that mediate T-cell activation in a Major Histocompatibility Complex (MHC) independent manner. Encouraging anti-tumor efficacy has been seen in r/r adult and pediatric ALL and in r/r CLL.
Primary Objective(s)	To evaluate the efficacy of CTL019 therapy from all manufacturing facilities as measured by overall remission rate (ORR) during the 3 months after CTL019 administration, which includes Complete Remission (CR) and CR with incomplete blood count recovery (CRi) as determined by independent review committee (IRC) assessment.
Key Secondary Objective	Objective 1: Evaluate the efficacy of CTL019 therapy from US manufacturing facility as measured by overall remission rate (ORR) during the 3 months after CTL019 administration, which includes CR and CR with incomplete blood count recovery (CRi) as determined by IRC assessment Objective 2: Evaluate the percentage of patients who achieve a best overall response (BOR) of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry among all patients who receive CTL019 from all manufacturing facilities Objective 3: Evaluate the percentage of patients who achieve a best overall response (BOR) of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry among all patients who receive CTL019 from US manufacturing facility
Secondary Objectives	Objective 1: To evaluate the percentage of patients who achieve CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment. Objective 2: To evaluate the percentage of patients who achieve CR or CRi and then proceed to SCT while in remission before Month 6 response assessment. Objective 3: To evaluate the duration of remission (DOR). Objective 4: To evaluate the relapse-free survival (RFS), event-free survival (EFS) and overall survival (OS). Objective 5: Evaluate the response at Day 28 +/- 4 days Objective 6: Evaluate the impact of baseline tumor burden on response Objective 7: Evaluate the quality of response using MRD disease assessments before treatment and at day 28 +/- 4 days after treatment using central assessment by flow

[redacted]

	cytometry and before SCT by local assessment (flow or PCR) Objective 8: To evaluate the safety of CTL019 therapy as measured by type, frequency and severity of adverse events and laboratory abnormalities. Objective 9: To characterize the *in vivo* cellular pharmacokinetic (PK) profile (levels, persistence, trafficking) of CTL019 cells in target tissues (blood, bone marrow, Cerebral Spinal Fluid (CSF), and other tissues if available). Objective 10: To describe the prevalence and incidence of immunogenicity to CTL019. Objective 11: Describe the effect of CTL019 therapy on Patient Reported Outcome (PRO) Objective 12: To derive a score to predict cytokine release syndrome. Objective 13: To describe the profile of soluble immune factors that may be key to cytokine release syndrome. Objective 14: To describe the levels of B and T cells (peripheral blood and bone marrow) prior to and following CTL019 infusion for safety monitoring. Objective 15: To assess the efficacy, safety and in vivo cellular pharmacokinetics of patients infused with CTL019 manufactured by [redacted]
Study design	This is a single arm, open-label, multi-center, phase II study to determine the efficacy and safety of CTL019 in pediatric patients with r/r B-cell ALL. The study will have the following sequential phases: Screening, Pre-Treatment (Cell Product Preparation & Lymphodepleting Chemotherapy), Treatment and Primary Follow-up, Secondary Follow-up (if applicable), and Survival Follow-up. The total duration of the study is 5 years from CTL019 cell infusion. After CTL019 infusion, efficacy will be assessed monthly for the first 6 months, then quarterly up to 2 years and semi-annually afterwards up to 5 years, or until patient relapse in the Treatment and Primary Follow-up phase. Safety will be assessed throughout the study. A post-study long term follow-up for lentiviral vector safety will continue under a separate destination protocol per health authority guidelines. At the beginning of the trial, a safety run-in stage will be conducted to enroll three patients for the purpose of assessing the acute safety profile of the Novartis designee manufactured CTL019 cell product. For the first three patients enrolled, following lymphodepleting chemotherapy and CTL019 infusion, safety profiles from the first 14 days post-infusion will be reported to the Health Authorities.
Population	The target population is comprised of pediatric patients with B-cell ALL who are chemo-refractory, relapsed after allogeneic SCT, or are otherwise ineligible for allogeneic SCT. Approximately 95 patients will be enrolled between the age of 3 years at the time of screening to the age of 21 years at the time of initial diagnosis. This will include at least 50 infused patients less than the age of 18 at the time of screening, at least 10 of which will be under the age of 10. Patients 18 years of age or older at screening will be limited to 10 total infused patients. When 10 patients ≥ 18 years of age have been infused, further enrollment in this age category will require Sponsor approval. Approximately 14 patients will be enrolled to ensure at least 10 patients are infused with CTL019 manufactured by the [redacted] Germany ([redacted]), a contract manufacturing organization (CMO).
Inclusion criteria	1. Relapsed or refractory pediatric B-cell ALL a. 2nd or greater Bone Marrow (BM) relapse OR b. Any BM relapse after allogeneic stem cell transplantation (SCT) and must be ≥ 6 months from SCT at the time of CTL019 infusion OR c. Primary refractory as defined by not achieving a CR after 2 cycles of a standard chemotherapy regimen or chemorefractory as defined by not achieving a CR after 1 cycle of standard chemotherapy for relapsed leukemia OR d. Patients with Philadelphia chromosome positive (Ph+) ALL are eligible if they are intolerant to or have failed 2 lines of tyrosine kinase inhibitor therapy (TKI), or if TKI therapy is contraindicated OR e. Ineligible for allogeneic SCT because of: • Comorbid disease

[redacted]

<table>
<tr><td></td><td>

Other contraindications to allogeneic SCT conditioning regimen
Lack of suitable donor
Prior SCT
Declines allogeneic SCT as a therapeutic option after documented discussion about the role of SCT with a bone marrow transplantation (BMT) physician not part of the study team

2. For relapsed patients, documentation of CD19 tumor expression in bone marrow or peripheral blood by flow cytometry within 3 months of study entry
3. Adequate organ function defined as:

Renal function defined as:
A serum creatinine based on age/gender as follows:

<table>
<tr><td></td><td colspan="2">Maximum Serum Creatinine (mg/dL)</td></tr>
<tr><td>Age</td><td>Male</td><td>Female</td></tr>
<tr><td>1 to < 2 years</td><td>0.6</td><td>0.6</td></tr>
<tr><td>2 to < 6 years</td><td>0.8</td><td>0.8</td></tr>
<tr><td>6 to < 10 years</td><td>1.0</td><td>1.0</td></tr>
<tr><td>10 to < 13 years</td><td>1.2</td><td>1.2</td></tr>
<tr><td>13 to < 16 years</td><td>1.5</td><td>1.4</td></tr>
<tr><td>≥ 16 years</td><td>1.7</td><td>1.4</td></tr>
</table>

Alanine Aminotransferase (ALT) ≤ 5 times the upper limit of normal (ULN) for age
Bilirubin < 2.0 mg/dL
Must have a minimum level of pulmonary reserve defined as ≤Grade 1 dyspnea and pulse oxygenation > 91% on room air
Left Ventricular Shortening Fraction (LVSF) ≥ 28% confirmed by echocardiogram (ECHO), or Left Ventricular Ejection Fraction (LVEF) ≥ 45% confirmed by echocardiogram or Multiple Uptake Gated Acquisition (MUGA) within 7 days of screening

4. Bone marrow with ≥ 5% lymphoblasts by morphologic assessment at screening
5. Life expectancy > 12 weeks
6. Age 3 years at the time of screening to age 21 years at the time of initial diagnosis
7. Karnofsky (age ≥ 16 years) or Lansky (age < 16 years) performance status ≥ 50 at screening
8. Signed written informed consent and assent forms if applicable must be obtained prior to any study procedures
9. Must meet the institutional criteria to undergo leukapheresis or have an acceptable, stored leukapheresis product
10. Once all other eligibility criteria are confirmed, must have a leukapheresis product of non-mobilized cells received and accepted by the manufacturing site. Note: Leukapheresis product will not be shipped to or assessed for acceptance by the manufacturing site until documented confirmation of all other eligibility criteria is received.</td></tr>
<tr><td>Exclusion criteria</td><td>1. Isolated extra-medullary disease relapse
2. Patients with concomitant genetic syndromes associated with bone marrow failure states: such as patients with Fanconi anemia, Kostmann syndrome, Shwachman syndrome or any other known bone marrow failure syndrome. Patients with Down Syndrome will not be excluded.
3. Patients with Burkitt’s lymphoma/leukemia (i.e. patients with mature B-cell ALL, leukemia with B-cell [surface Immunoglobulin (sIg) positive and kappa or lambda restricted positivity] ALL, with French-American-British [FAB] L3 morphology and /or a MYC translocation)
4. Prior malignancy, except carcinoma in situ of the skin or cervix treated with</td></tr>
</table>

[redacted]

	curative intent and with no evidence of active disease 5. Treatment with any prior gene therapy product 6. Has had treatment with any prior anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy 7. Active or latent hepatitis B or active hepatitis C (test within 8 weeks of screening), or any uncontrolled infection at screening 8. Human Immunodeficiency Virus (HIV) positive test within 8 weeks of screening 9. Presence of grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD) 10. [Retired from Amended Protocol Version 01] 11. Active Central Nervous System (CNS) involvement by malignancy, defined as CNS-3 per National Comprehensive Cancer Network (NCCN) guidelines. Note: Patients with history of CNS disease that has been effectively treated will be eligible 12. Patient has received an investigational medicinal product within the last 30 days prior to screening 13. Pregnant or nursing (lactating) women. NOTE: female study participants of reproductive potential must have a negative serum or urine pregnancy test performed within 48 hours before infusion 14. [Retired from Amended Protocol Version 02] 15. [Retired from Amended Protocol Version 02] 16. Women of child-bearing potential (defined as all women physiologically capable of becoming pregnant) and all male participants, unless they are using highly effective methods of contraception for a period of 1 year after the CTL019 infusion. Highly effective contraception methods include: a. Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are NOT acceptable methods of contraception) b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment c. Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient d. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception e. Use of intrauterine devices (IUDs) are excluded due to increased risks of infection and bleeding in this population. However, IUD inserted prior to consent may remain in place, and a second method of contraception is mandated. f. In case of use of oral contraception, women must be stable on the same pill for a minimum of 3 months before taking study treatment Women who are not of reproductive potential (defined as either <11 years of age, Tanner Stage 1, post-menopausal for at least 24 consecutive months or have undergone hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy) are eligible without requiring the use of contraception. Women who are not yet of reproductive potential are to agree to use acceptable forms of contraception when they reach reproductive potential if within 1 year of CTL019 or if CAR cells are present in the blood by PCR. Acceptable documentation includes written or oral documentation communicated by clinician or clinician's staff of one of the following: a. Demographics show age <11 b. Physical examination indicates Tanner Stage 1

[redacted]

	c. Physician report/letter d. Operative report or other source documentation in the patient record e. Discharge summary f. Follicle stimulating hormone measurement elevated into the menopausal range 17. The following medications are excluded: a. **Steroids:** Therapeutic systemic doses of steroids must be stopped > 72 hours prior to CTL019 infusion. However, the following physiological replacement doses of steroids are allowed: <12 mg/m^2/day hydrocortisone or equivalent b. **Allogeneic cellular therapy:** Any donor lymphocyte infusions (DLI) must be completed > 6 weeks prior to CTL019 infusion c. **GVHD therapies:** Any systemic drug used for GVHD must be stopped > 4 weeks prior to CTL019 infusion to confirm that GVHD recurrence is not observed (e.g. calcineurin inhibitors, methotrexate or other chemotherapy drugs, mycophenolyate, rapamycin, thalidomide, or immunosuppressive antibodies such as anti-CD20 (rituximab), anti-tumor necrosis factor [anti-TNF], anti-interleukin 6 [anti-IL6] or anti-interleukin 6 receptor [anti-IL6R], systemic steroids) d. **Chemotherapy:** • Tyrosine kinase inhibitors and hydroxyurea must be stopped > 72 hours prior to CTL019 infusion • The following drugs must be stopped > 1 week prior to CTL019 infusion and should not be administered concomitantly or following lymphodepleting chemotherapy: vincristine, 6-mercaptopurine, 6-thioguanine, methotrexate <25 mg/m^2, cytosine arabinoside < 100 mg/m^2/day, asparaginase (non-pegylated) • The following drugs must be stopped > 2 weeks prior to CTL019 infusion: salvage chemotherapy (e.g. clofarabine, cytosine arabinoside > 100 mg/m^2, anthracyclines, cyclophosphamide, methotrexate ≥ 25 mg/m^2), excluding the required lymphodepleting chemotherapy drugs • Pegylated-asparaginase must be stopped > 4 weeks prior to CTL019 infusion e. **CNS disease prophylaxis:** • CNS prophylaxis treatment must be stopped > 1 week prior to CTL019 infusion (e.g. intrathecal methotrexate) f. Radiotherapy • Non-CNS site of radiation must be completed > 2 weeks prior to CTL019 infusion • CNS directed radiation must be completed > 8 weeks prior to CTL019 infusion g. **Anti T-cell Antibodies:** Administration of any T cell lytic or toxic antibody (e.g. alemtuzumab) within 8 weeks prior to CTL019 is prohibited since residual lytic levels may destroy the infused CTL019 cells and/or prevent their in vivo expansion. If such an agent has been administered within 8 weeks prior to CTL019, contact the Sponsor, consider consultation with an pharmacology expert, and consider measuring residual drug levels, if feasible, prior to CTL019 infusion.
Investigational and reference therapy	A target per-protocol dose of CTL019 transduced cells will consist of a single infusion of 2.0 to 5.0 x 10^6 CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 1.0 to 2.5 x 10^8 CTL019 transduced viable T cells (for patients > 50 kg). The following cell dose ranges may be infused if all other safety release criteria are met: 0.2 to 5.0 x 10^6 CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 0.1 to 2.5 x 10^8 CTL019 transduced viable T cells (for patients > 50 kg)
Efficacy assessments	**Primary:** ORR, which includes CR and CRi, as determined by assessments of peripheral blood, bone marrow, CNS symptoms, physical exam (PE) and CSF. The primary endpoint will be based on the IRC assessment. The local investigator's

[redacted]

	assessed results will be used for sensitivity analysis. **Secondary:** Patients with CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment, patients who achieve CR or CRi and then proceed to SCT while in remission prior to Month 6 response assessment, Minimal residual disease, duration of remission, relapse-free survival, event-free survival, and overall survival
Safety assessments	Adverse events and laboratory abnormalities (type, frequency and severity) Immunogenicity assessments : a. prevalence of immunogenicity against CTL019 (pre-existing), both humoral and cellular b. incidence of immunogenicity against CTL019, both humoral and cellular c. proportion of patients with transient anti-CTL019 antibody assay titers d. proportion of patients with sustained anti-CTL019 antibody assay titers
Other assessments	Pharmacokinetic assessments planned for this trial include: • Detection of CTL019 in blood, bone marrow and CSF (if available) by Quantitative Polymerase Chain Reaction (q-PCR). • Expression of CTL019 detected by flow cytometry in blood and bone marrow • Maximum Concentration (Cmax), Time of Peak Concentration (Tmax), Area Under the Curve (AUCs) and other relevant PK parameters of CTL019 in blood, bone-marrow, CSF (if available). • Maximum extent of expansion of CTL019 in blood • Persistence of CTL019 in blood, bone marrow and CSF Exploratory objectives and biomarker assessments planned for this trial include: • Determine the incidence and pattern of tumor clonal evolution ([redacted]) • T cell trafficking (CTL019 immunophenotyping) • Quantify the relationship between 1) CTL019 cell product/leukapheresis product [redacted] 2) other cell product/leukapheresis product characteristics and clinical endpoints (efficacy, safety, PK) • Describe the effect of anti-cytokine therapy on Cytokine Release Syndrome (CRS), CTL019 Pharmacokinetics/Pharmacodynamics (PK/PD), and tumor response • Explore the relationship between CRS, initial tumor burden, clinical tumor response, and PK/PD parameters • [redacted] • To describe hospital resource utilization
Data analysis	**Primary endpoints:** An interim analysis will be performed when the first 50 patients who receive CTL019 have completed 3 months from study day 1 infusion or discontinued earlier. The final analysis of the primary endpoint will be performed after all patients infused with CTL019 and have completed 3 months follow-up from study day 1 infusion or discontinued earlier. Selected efficacy and safety analyses will be updated annually. A final Clinical Study Report (CSR) will be produced once all patients complete the study. The primary efficacy endpoint, ORR will be analyzed based on the data observed by IRC in the interim efficacy analysis set (IEAS) or the full analysis set (FAS) at time of interim and final analysis respectively. The primary efficacy analysis will be performed by testing the null hypothesis of the ORR being less than or equal to 20% against the alternative hypothesis the ORR is greater than 20% at overall one-sided 2.5% level of significance. The ORR will be summarized along with the 2-sided exact Clopper-Pearson confidence intervals with coverage level determined by the O'Brien-Fleming type α-spending approach according to Lan-DeMets. The study will be considered successful if the lower bound of the 2-sided exact confidence interval for ORR is greater than 20%, so that the null hypothesis that the ORR is less or equal to 20% can be rejected. Sensitivity analyses will be performed on the Enrolled Set, the per-protocol set (PPS)

[redacted]

	and with all patients who satisfy all clinical eligibility criteria (defined as all inclusion/exclusion criteria except that which pertains to the leukapheresis product) using the same method as described above. Additional sensitivity analysis will be performed using the ORR as assessed by local investigators. **Secondary endpoints:** Key secondary endpoints include ORR in all patients who received CTL019 from US manufacturing facility, and the rate of remission with MRD negative bone marrow in patients who received CTL019 from all manufacturing facilities and separately in patients who received CTL019 from US manufacturing facility. Hypotheses testing of key secondary endpoints will follow a hierarchical testing scheme so that the family-wise type I error rate will be controlled at one-sided 2.5% level. Analysis of other secondary or exploratory endpoints will be descriptive and may include summary statistics such as means, standard deviations, 95% confidence intervals, if applicable. Cumulative Incidence Functions (CIF), Kaplan-Meier curves and median time to event will be presented for time-to-event variables (DOR, RFS, EFS and OS), if appropriate. **Sample size:** In a previous study of clofarabine in pediatric patients with r/r B-cell ALL who have had 2 or more prior regimens, the reported ORR was 20%. Based on the null hypothesis of ORR ≤ 20% and alternative hypothesis of ORR >20%, up to 76 patients in the FAS will provide more than 95% power to demonstrate statistical significance at one-sided 2.5% level of significance, if the underlying ORR is 45%. Accounting for the patients to assess CTL019 manufactured from the [redacted], and assuming 20% to 25% enrolled patients will not be infused due to reasons such as CTL019 product manufacturing issues, worsening of patient's condition, etc., approximately 95 patients need to be enrolled.
Key words	Relapsed/refractory ALL, relapsed ALL post allogeneic SCT, CTL019

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

B cell malignancies comprise a heterogeneous group of neoplasms including acute lymphoblastic leukemias (ALL), chronic lymphocytic leukemias (CLL), and a vast majority of non-Hodgkin's lymphomas (NHL). An estimated 91,000 new cases of lymphocytic leukemia and NHL were diagnosed in the US in 2012 (National Cancer Institute 2013). There were 66,371 lymphoid malignancies registered in 2000-2002 by 44 European cancer registries (Sant et al 2010). The majority of these malignancies are of B cell origin (Mitchell et al 2012).

ALL is more commonly seen in children although can occur at any age. ALL represent 75% to 80% of acute leukemias among children, therefore, making it the most common form of childhood leukemia (The Leukemia & Lymphoma Society 2009). The median age at diagnosis for ALL is 13 years; 60% of patients are diagnosed at younger than 20 years of age, whereas 23% are diagnosed at 45 years or older. Among children, B-cell lineage ALL constitutes approximately 88% of leukemia cases.

Current treatment for B cell malignancies include combinations of chemotherapy, radiation therapy, bone marrow transplantation, or peripheral blood and cord blood stem cell transplantation (SCT). Despite these treatment modalities, many relapsed patients remain incurable. Initial chemotherapy is typically administered over a 2 to 3 year period. With current multi-agent treatment regimens, the cure rate among children with ALL is > 80%. Most patients (>85%) with relapsed ALL will achieve a second remission (Ko et al 2010); however, the challenge remains to maintain remission. Most children who relapse once will relapse again, and will ultimately succumb to their disease. Leukemia is still the leading cause of death in pediatric oncology (Tallen et al 2010). Refractory ALL [never achieving a complete remission (CR)] in adults or children has a dismal prognosis and these patients do not benefit from SCT. Thus relapsed or refractory (r/r) ALL patients, both adult and pediatric, have significant unmet medical needs.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of CTL019

Immunotherapy is a treatment that involves activating or enhancing the immune system to help fight diseases including cancer. Adoptive immunotherapy with allogeneic donor leukocytes (e.g. donor lymphocyte infusion) has potent anti-leukemic effects, however the benefit is confined largely to patients with myeloid leukemias, as B-ALL has a durable remission rate of less than 10% (Kolb et al 1995), and often at the cost of substantial morbidity due to GVHD (Appelbaum 2001, Sullivan 1989).

Adoptive T-cell therapy is one particular approach that involves engineering T-cell receptors (TCRs) to bind to specific antigens present on tumor cells. These modified TCRs, known as

[redacted]

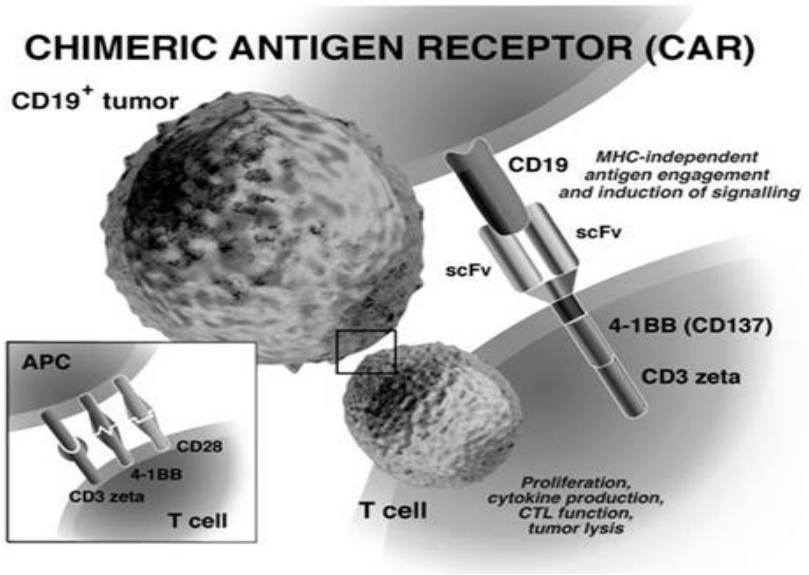
chimeric antigen receptors (CARs), allow the immune system to specifically target and destroy tumor cells in a MHC independent manner (Mellman et al 2011).

A very promising potential target antigen for B cell malignancies is CD19, a cell-surface protein whose expression is restricted to B cells and their precursors (Sadelain 2003, Brentjens 2010, Porter 2011). CD19 is not expressed on hematopoietic stem cells or non-B cell tissues. It is a member of the immunoglobulin (Ig) superfamily and a component of a cell surface signal transduction complex that regulates signal transduction through the B cell receptor (Ledbetter 1988, Stamenkovic 1988, Fearon 2000). Mice lacking CD19 have decreased number of B cells in peripheral lymphoid tissues, decreased B cell response to oral vaccines and mitogens, and decreased serum Ig levels (Ledbetter 1988, Stamenkovic 1988, Tedder 1989, Fearon 2000).

First generation CARs contain the TCR activation signal domain consisting of TCRζ. Second generation CARs contain costimulatory signaling domains as well: either CD28 or 4-1BB. The 3rd generation CARs contain further advancements such as double costimulatory modules comprised of CD28, 4-1BBplus TCRζ (June 2007, June 2009, Kohn 2011).

CTL019 (CART-19) is an adoptive cellular immunotherapy that uses the autologous peripheral blood T cells that have been genetically modified *ex vivo* to target CD19 on the surface of B cells. As shown in Figure 1-1, the CAR approach uses genetically programmed lymphocytes transduced with chimeric receptor genes to combine the effector functions of T lymphocytes with the ability of antibodies to recognize predefined surface antigens with high specificity in a non-MHC restricted manner (Gross 1989, Pinthus 2003). These receptors have the ability to recognize intact membrane proteins independent of antigen processing. The tumor antigen binding function of CAR is usually accomplished by the inclusion of a single chain variable fragment (scFv) antibody, containing the heavy chain variable domain (V_H) and light chain variable domain (V_L) chains joined by a peptide linker of about 15 residues in length (Mullaney et al 2001).

Figure 1-1 CTL019 chimeric antigen receptor design



[redacted]

Early results from ongoing clinical trials of CTL019 in r/r CLL and r/r ALL have shown promising and durable anti-tumor efficacy (Porter 2011, Grupp 2013, Maude 2014). It is anticipated that CTL019 may offer a therapeutic alternative for patients with r/r B cell malignancies who are either SCT ineligible or who have relapsed after SCT, which may offer a greater durability of remission than current salvage therapies. In the future, CTL019 may also have the potential to replace SCT as a therapeutic choice, expanding patient eligibility by obviating the need for matched donors along with potentially lower rates of upfront mortality and morbidity.

1.2.1.1 Non-clinical experience

Extensive literature supports the use of engineered T cells for tumor immunotherapy in rodent tumor models (Calogero 2000, Clay 2002, Hombach 2002, Pule 2003, Sadelain 2003). Others have used electroporation or retroviral vectors to create CAR T cells and have shown *in vivo* safety and efficacy of adoptively transferred T cells in immunodeficient mouse models (Willemsen 2000, Roessig 2002, Brentjens 2003, Cooper 2003, Serrano 2006). The incorporation of costimulatory signaling modules such as CD28 and 4-1BB in second generation CARs increases potency of the engineered T cells in pre-clinical studies (Finney 1998, Krause 1998, Eshhar 2001, Maher 2002, Finney 2004, Friedmann-Morvinski 2005, Brentjens 2010). The pre-clinical data supporting CAR T cell persistence, expansion and anti-tumor efficacy have been published (Gross 1992, Milone 2009).

1.2.1.2 Clinical experience

For a summary of ongoing human studies with CTL019 (patients treated, disease indication, CTL019 dosing), please refer to the most current Investigator Brochure.Initial dosing in adults and children, for safety reasons, used a split infusion schedule of escalating doses. However, the majority of patients in the two phase I studies received CTL019 as a single one time infusion or two sequential infusions due to the onset of fevers and other clinical events precluding further infusions. For pediatric patients, cells are dosed per kg body weight where dosing in adults does not consider body weight.

Safety

Pediatric r/r Acute Lymphoblastic Leukemia

Toxicities seen in pediatric r/r ALL patients include expected chemotherapy related adverse events (AE) and CTL019 related events of tumor lysis syndrome (TLS) and CRS/macrophage activation syndrome (MAS) (Grupp 2013, Maude 2014). TLS and CRS/MAS in ALL patients typically occurred within days to a week following CTL019 infusion and correlated with peak *in vivo* CTL019 cell expansion. TLS complications were managed as per standard of care including prophylactic allopurinol (in patients with elevated uric acid or high tumor burden) and fluids, and rasburicase as needed. CRS/MAS has been managed in pediatric ALL patients with supportive care and when needed, tocilizumab (anti-IL-6 receptor monoclonal antibody) therapy. Since CRS mechanistically is believed to possibly be a required part of the antitumor mechanism of *in vivo* CTL019 cell expansion and tumor killing, tocilizumab was administered for CRS only after symptoms became moderate or severe. This included worsening respiratory distress, pulmonary infiltrates, increasing oxygen requirement (defined

[redacted]

as high-flow oxygen and/or need for mechanical ventilation), hemodynamic instability despite intravenous fluids and moderate/high dose vasopressor support, and/or rapid clinical deterioration. Preliminary data supports that management with tocilizumab does not appear to diminish CTL019 cell expansion, therefore tocilizumab should be administered for CRS when symptoms warrant treatment per the CRS management algorithm (Figure 6-1). Steroids following CTL019 infusion were avoided and given only under life threatening situations due to their known lympholytic effects. Clinical responses do not appear to correlate with prior relapsed or refractory status of the patient. CRS severity appears to correlate with pre-infusion tumor burden in pediatric ALL but not with CTL019 transduced cell numbers within the range of cell doses infused. More severe CRS is associated with earlier clinical onset of CRS related symptoms in pediatric r/r ALL patients. Refer to Section 6.2.4.2 for guidance related to CRS management and the Investigator Brochure for additional safety information.

As of May 2015, 51 pediatric ALL r/r patients were treated on the CHP959 Phase I study with either one, two, or three doses of CTL019 with split dosing (10%, 30%, 60%). The age range of patients was 4 to 22 years. CRS of variable severity was seen in 46 pediatric patients out of the 51. Of the 46 patients with CRS, 24 patients had Grade 3 or 4 CRS (47.1%). Median time to CRS onset was three days (day 1 to 11) and median time to CRS resolution was 11 days (day 6 to 24). CRS that developed into severe Grade 4 (defined as hypotension requiring the use of two or more vasopressors or respiratory failure requiring mechanical ventilation) had an initial onset at median of day 2 after infusion, whereas CRS that did not develop into Grade 4 (non-severe) had an initial onset at a median of day 5 after infusion. Fifteen patients (33%) required tocilizumab (one to three doses) in addition to supportive care for management of CRS which resulted in defervescence and stabilization of blood pressure, with improvement (weaning from vasopressor support) over a period of 1 to 3 days. Nineteen (42%) patients required admission to the intensive care unit (ICU) with 5 patients requiring high dose vasopressor support and 6 patients requiring mechanical ventilation. Disseminated intravascular coagulation requiring blood product support was seen in 5 patients and reversible encephalopathy was seen in 16 patients. CRS seen in pediatric patients was manageable with supportive care, and, when needed, tocilizumab. All pediatric patients recovered fully with complete reversal of symptoms and a normalization of laboratory results. Patients achieving a CR also experienced B-cell aplasia and hypogammaglobulinemia, which was supported with periodic intravenous immune globulin infusions as per local guidelines. GVHD was not seen in the patients who had previously undergone an allogeneic SCT with known donor chimerism.

Maude et al (2014) reported that 13/30 CTL019 treated patients (25 pediatric and 5 adult) in the Phase I trials as of March 2014 had neurologic toxic effects, which ranged from delirium during the period of high fevers to global encephalopathy with one or more of the following: aphasia, confusion, delirium, and hallucinations. Six patients had delayed encephalopathy that occurred after high fevers had resolved and was independent of the severity of the CRS and whether the patient had received prior tocilizumab therapy. Symptoms were self-limiting (lasting 2 to 3 days and resolving over 2 to 3 days), and they resolved fully without further intervention or apparent long-term sequelae. One patient with encephalopathy had two seizures that may have been caused by concomitant electrolyte abnormalities. Several patients had normal computed tomographic or magnetic resonance imaging of the head and lumbar puncture that was negative for infection or leukemia.

[redacted]

Evaluation of the first 3 r/r pediatric ALL patients treated with Novartis manufactured CTL019 did not reveal any unexpected or unmanageable acute toxicities within the 14 to 28 days following CTL019 infusion. All three patients met the intended target dose of 2 to 5 x 10^6 transduced viable T cells/kg body weight. The acute toxicities observed were similar with those observed in r/r pediatric ALL patients treated in the CTL019B2205J multicenter and CHP959 single center studies under the Penn IND and manufactured by the Clinical Cell and Vaccine Production Facility (CVPF) at the University of Pennsylvania.

Responding CLL and ALL patients demonstrated detectable and prolonged persistence of CTL019 transduced cells in the setting of CR; over 2 years in one ALL patient, and over 4 years in two CLL patients (Porter 2011, Grupp 2013, Maude 2014).

Adult r/r ALL

As of May 2015, 21 adult r/r ALL patients have been treated on a phase I trial (UPCC04409 protocol, NCT01029366) or phase II trial (UPCC21413 protocol, NCT02030847) under the Penn IND. The age range is 20 to 71 years. CRS was seen in 20 of 21 patients. Seventeen patients (81%) had Grade 3 or 4 CRS and 17 (85%) of these patients required anti-cytokine therapy with tocilizumab.

The phase II adult r/r ALL UPCC21413 trial utilized a single infusion of a higher dose of CTL019 cells. Among the first six patients treated, three deaths were attributable to Grade 5 refractory CRS in the setting of significant concomitant infections. The subsequent six patients on this trial were then treated with a reduced cell dose of CTL019. Two early deaths out of these six subsequent patients were seen with the lower dose of CTL019 cells, however, CRS in these two cases was deemed not to be refractory to intervention. The cause of death was cerebral hemorrhage in one patient and sepsis in the other patient. The last three patients were treated with the same reduced cell dose of CTL019 using a split dosing model. No early deaths were observed.

Other institutions have also reported fatal SAEs in adult patients associated with the use of CD19 CARs. In one of these fatal SAEs, death occurred 44 hours post-CD19 CAR T cell infusion. The investigators concluded that concomitant sepsis was the most likely cause of death and attributed the etiology of the death as “possibly related” to CAR T cell infusion (Brentjens 2010). Two other fatal SAEs in adult patients have been reported by other institutions outside the University of Pennsylvania. Each of these deaths occurred within the first two weeks of CAR infusion.

Efficacy (Pediatric r/r ALL)

As of May 2015, of the 51 r/r pediatric ALL patients treated in the CHP959 Phase I study, 46/51 (90%) achieved complete remission (CR or CRi). Similar response rates were seen in patients with or without prior allogeneic stem cell transplant. All responding patients developed B-cell aplasia. The administered dose range per kg was 1.0 x 10^6 to 17.3 x 10^6 transduced CTL019 cells/kg. The total transduced CTL019 cells administered was 0.3 x 10^8 to 9.1 x 10^8 CTL019 cells.

[redacted]

2 Rationale

2.1 Study rationale and purpose

Outcome remains poor for patients with r/r pediatric B-cell lineage acute lymphoblastic leukemia (B-cell ALL). Treatment options for r/r B-cell ALL include further treatment with salvage chemotherapy, second allogeneic stem cell transplantation (SCT) or supportive care. Therapy in this population is not curative with an overall survival of 3 to 6 months (Smith 2010, Tallen 2010, Martin 2012, Ko 2010, Duval 2010, Oudot 2008). As an example, clofarabine was approved by the Food and Drug Administration (FDA) for the treatment of pediatric patients with r/r ALL after at least 2 prior therapeutic regiments. The overall remission rates were 30% for ALL and 38% for Acute Myeloid Leukemia (AML) in Phase I studies (Jeha et al 2004); 30% (20% CR or complete remission with incomplete platelet recovery [CR_p] and 10% Partial Remission [PR]) for ALL and 26% for AML in Phase II studies (Jeha et al 2006). The median duration of remission for patients with ALL who achieved at least a partial remission was 9.7 weeks (range 7 to 335 days) in the Phase II study.

CD19 has emerged as an attractive therapeutic target because it is widely expressed on normal and malignant B-cells throughout B-cell maturation but not on pluripotent stem cells or non–B-cell tissues. The development of CAR T cells to target CD19+ cells (CART19 or CTL019) provides an innovative new approach to these malignancies. This approach involves recipient-derived T cells that are genetically modified *ex vivo* via lentiviral transduction to express a CD19 antigen recognition domain attached to intracellular signaling domains that mediate T-cell activation in an MHC independent manner. Encouraging anti-tumor efficacy has been seen in r/r adult and pediatric ALL and in r/r CLL.

2.2 Rationale for the study design

This is a single arm, multi-center, phase II study to determine the efficacy and safety of CTL019 in pediatric patients with relapsed or refractory B-cell ALL. A single arm study design is supported by the absence of effective therapies in this setting, and high unmet medical needs. This study will enroll approximately 95 patients to allow at least 50 infused patients less than the age of 18 at the time of screening, at least 10 of which will be under the age of 10. Patients 18 years of age or older at screening will be limited to 10 total infused patients. When 10 patients ≥ 18 years of age have been infused, further enrollment in this age category will require Sponsor approval. Approximately 14 patients will be enrolled to ensure at least 10 patients are infused with CTL019 manufactured by the [redacted]. After assessment of eligibility, patients qualifying for the study will be enrolled and start lymphodepleting chemotherapy as indicated per protocol, followed by a single dose of CTL019 transduced cells.

Previous clinical data with CTL019 therapy has been generated using cell product manufactured at the Cell and Vaccine Production Facility (CVPF) at the University of Pennsylvania. The current trial will utilize product manufactured by Novartis or designee. *In vitro* studies assessing the comparability of these two products will have been completed prior to initiation of this protocol. A limited **safety run-in stage** will be conducted at the beginning of this trial. These patients will be included in the total targeted patient population.

[redacted]

The efficacy of CTL019 will be evaluated through the primary endpoint of ORR (ORR = CR + CRi) as determined by Independent Review Committee (IRC) assessment, including CR and CRi. The choice of ORR as the primary endpoint is based on evidence that ORR: 1) Is a standard outcome measurement in ALL; and 2) the established correlation with long-term outcome (Cheson 2003, Appelbaum 2007, NCCN v13 2013).

2.2.1 Rationale for lymphodepletion

Adoptive immunotherapy strategies may be able to capitalize on homeostatic T cell proliferation (Dummer et al 2002), a recent finding that naive T cells begin to proliferate and differentiate into memory-like T cells when total numbers of naive T cells are reduced below a certain threshold (Goldrath 1999, Surh 2000). Host lymphodepletion may enhance the effectiveness of adoptively transferred T cells (Dummer et al 2002). Homeostatic T cell proliferation can lead to activation of certain immune cell subsets (King et al 2004), providing a clue to improved anti-tumor responses. T cells can undergo up to seven rounds of cell division after being deprived of contact with antigen presenting cells (Kaech 2001, van Stipdonk 2001). Lymphodepletion eliminates regulatory T-cells and other competing elements of the immune system that act as "cytokine sinks", enhancing the availability of cytokines such as IL-7 and IL-15 (Klebanoff et al 2005). This hypothesis has been tested clinically in patients with metastatic melanoma refractory to conventional treatments (Dudley et al 2002). The patients received a lymphodepleting conditioning regimen consisting of cyclophosphamide (60 mg/kg x 2 days) and fludarabine (25 mg/m^2 x 5 days) prior to adoptive transfer of T cells. Patients with myeloma have been treated with CARs and lymphopenia after lymphodepleting chemotherapy, and observed improved engraftment (Laport 2003, Rapoport 2005). In this protocol, it is proposed to infuse CTL019 T cells into patients that are rendered lymphopenic as a result of cytotoxic chemotherapy. Recent data indicates that the increased antitumor efficacy of adoptive transfer following host conditioning is more than simply "making room" because the quantitative recovery of adoptively transferred T cells in mice reveals that *in vivo* proliferation following adoptive transfer is identical in mice with or without previous irradiation (Palmer et al 2004).

In ongoing CTL019 pediatric ALL studies, 13 out of the first 16 patients infused with CTL019 cells received a lymphodepleting conditioning regimen prior to adoptive transfer of T cells. Six patients received a lymphodepleting conditioning regimen consisting of cyclophosphamide and fludarabine, five patients received cyclophosphamide and etoposide, one patient received etoposide and cytarabine and one patient received cyclophosphamide alone. Of the three patients who did not receive a lymphodepleting conditioning regimen, two patients presented with Absolute Lymphocyte Count (ALC) < 1000 at the time of infusion.

2.3 Rationale for dose and regimen selection

Animal studies support a threshold dose of CTL019 cells and therefore the initial clinical dose selection was within the range of 1 x 10^7 to 1 x10^9 CTL019 transduced cells (Milone et al 2009). Please see IB for further information on preclinical studies. For safety reasons, initial phase I cell dosing was divided among three split infusions (10%, 30% and 60% of the total cell dose). Of the 26 pediatric ALL patients that had a complete remission, 13 patients

[redacted]

received a single infusion due to the onset of fevers, yet CRs were observed with either 1 to 3 infusions.

In phase I CLL studies, patients have shown responses after a single infusion or multiple infusions. In the phase II CLL trial, the dose has been given as a single infusion of 1 to 5 x 10^7 or 1 to 5 x 10^8 CTL019 transduced cells to study dose optimization. This single infusion was clinically well tolerated. No significant differences have been seen in responses or toxicity between these two doses. In responding CLL patients with CR or lasting PR, the CTL019 transduced cell numbers infused have ranged from 1.4 x 10^7 to 1.1 x 10^9 cells.

From the data collected to date in patients with CLL and ALL, there does not appear to be a discernible dose-response relationship with CTL019 transduced cell numbers infused. This is likely the result of CTL019 transduced cells ability to proliferate and expand extensively (e.g. 1000 to >10,000 fold) *in vivo*. Thus, the administered dose may underestimate the number of CTL019 cells *in vivo* following engraftment and expansion and will vary from patient to patient. Additional considerations in this dose selection take into account the manufacturing feasibility of producing adequate numbers of CTL019 transduced cells.

In pediatric ALL patients who were treated in the CHP959 study, patients received once, two or three CTL019 infusions. Tumor responses were seen with each of these dosing schedules.Nineteen patients within the CHP959 study received only a single infusion of CTL019 due to the onset of fever with a cell range of 1.1 x 10^6 to 6.3 x10^6 CTL019 cells per kg with an acceptable safety profile. At the lower end of this dose range there is concern that doses less than 2 x 10^6 cells/kg may be associated with a lack of response or CR with an early relapse however the data at lower doses is limited.

Several patients received total CTL019 cell dose of over 5 x 10^8 cells (e.g. 6.8, 7.8 and 9.1 x 10^8 total CTL019 cells). Since the experience with these higher doses is more limited, a cut off of 2.5 x 10^8 cells as a maximum dose, based upon a weight >50 kg, is proposed. Manufacturing consideration and practicality were also considered in the dosing selection.

Therefore, the targeted per-protocol CTL019 cell dose range for pediatric ALL patients ≤ 50 kg is 2.0 to 5.0 x 10^6 autologous CTL019 transduced viable T cells per kg body weight. For patients > 50 kg, the target dose is 1.0 to 2.5 x 10^8 autologous CTL019 transduced viable T cells.

2.3.1 Allowable infused cell dose range of CTL019 product

The allowable cell dose ranges are as follows:

- Patients ≤ 50 kg: 0.2 to 5.0 x 10^6 autologous CTL019 transduced viable T cells per kg body weight
- Patients > 50 kg: 0.1 to 2.5 x 10^8 autologous CTL019 transduced viable T cells

Products falling below the minimum values in the above allowable cell dose ranges will not be released for infusion.

2.4 Rationale for choice of combination drugs

Not applicable.

[redacted]

2.5 Rationale for choice of comparators drugs

Not applicable.

2.6 Risks and benefits

The risk to subjects in this trial may be minimized by compliance with the eligibility criteria, pre-infusion criteria, CRS treatment algorithm, study procedures, and close clinical monitoring. There may be unforeseen risks with CTL019 which could be serious or potentially life threatening. Refer to [Investigator Brochure] for further details.

Based on the observed efficacy as assessed by high response rates and lasting remissions of CTL019 therapy in pediatric patients with r/r B cell ALL, the potential benefit of CTL019 therapy in the target patient population treated in study CCTL019B2202 outweighs the potential risks of the therapy. CRS is identified as a clinically significant risk of CTL019 treatment. To address this risk a CRS treatment algorithm and CRS grading scale has been specifically developed and utilized for CTL019. In addition, logistical measures are also recommended to further manage this safety risk: patients are required to stay near the treatment site for the first 21 days, patients are required to stay with a caregiver and record twice daily temperatures during first two weeks, and patients/caregivers are required to carry patient identification card with investigator contact information. Refer to Section 6.2.4.2 for details on CRS management.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
Evaluate the efficacy of CTL019 therapy from all manufacturing facilities as measured by overall remission rate (ORR) during the 3 months after CTL019 administration, which includes CR and CR with incomplete blood count recovery (CRi) as determined by IRC assessment	ORR (= CR + CRi) assessment; See Appendix 1 for response definition	Refer to Section 10.4.
Key secondary		
Evaluate the efficacy of CTL019 therapy from US manufacturing facility as measured by overall remission rate (ORR) during the 3 months after CTL019 administration, which includes CR and CR with incomplete blood count recovery (CRi) as determined by IRC assessment	ORR (= CR + CRi) assessment; See Appendix 1 for response definition	Refer to Section 10.5.1.1
Evaluate the percentage of patients who achieve a best overall response (BOR) of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry among all patients who receive CTL019 from all manufacturing facilities	Percentage of patients with BOR of CR or CRi with MRD negative bone marrow by flow cytometry during the 3 months after CTL019 infusion among all patients who are infused with CTL019 from all manufacturing facilities	Refer to Section 10.5.1.2
Evaluate the percentage of patients who achieve a best overall response (BOR) of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry among all patients who receive CTL019 from US manufacturing facility	Percentage of patients with BOR of CR or CRi with MRD negative bone marrow by flow cytometry during the 3 months after CTL019 infusion among all patients who are infused with CTL019 from US manufacturing facility	Refer to Section 10.5.1.3.
Other secondary		
Evaluate the percentage of patients who achieve CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment	Percentage of patients who achieve CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment	Refer to Section 10.5.2.1
Evaluate the percentage of patients who achieve CR or CRi and then proceed to SCT while in remission before Month 6 response assessment	• Percentage of patients who achieve CR or CRi and then proceed to SCT while in remission prior to Month 6 response assessment • In addition, all patients that proceed to SCT after CTL019 infusion will be described	Refer to Section 10.5.2.2.

[redacted]

Objective	Endpoint	Analysis
Evaluate the duration of remission (DOR)	• DOR, i.e. the time from achievement of CR or CRi, whichever occurs first, to relapse or death due to ALL • Site of involvement of subsequent relapse will be summarized	Refer to Section 10.5.2.3.
Evaluate the relapse-free survival (RFS)	RFS, i.e. the time from achievement of CR or CRi whichever occurs first to relapse or death due to any cause during CR or CRi	Refer to Section 10.5.2.4.
Evaluate the event-free survival (EFS)	EFS, i.e. the time from date of CTL019 infusion to the earliest of death, relapse or treatment failure	Refer to Section 10.5.2.5.
Evaluate the overall survival (OS)	OS, i.e. the time from date of CTL019 infusion to the date of death due to any reason	Refer to Section 10.5.2.6.
Evaluate the response at Day 28 +/- 4 days	Proportion of patients attaining CR or CRi at Day 28 +/- 4 days post CTL019 infusion	Refer to Section 10.5.2.8.
Evaluate the impact of baseline tumor burden on response	Response as a function of baseline tumor burden (tumor load) (MRD, extramedullary disease, etc)	Refer to Section 10.5.2.9.
Evaluate the quality of response using MRD disease assessments before treatment and at day 28 +/- 4 days after treatment using central assessment by flow cytometry and before SCT by local assessment (flow or PCR)	MRD quantitative result (% leukemic cells) and qualitative result (positive/negative)	Refer to Section 10.5.2.10.
Evaluate the safety of CTL019 therapy	Type, frequency and severity of adverse events and laboratory abnormalities	Refer to Section 10.5.3.
Characterize the *in vivo* cellular pharmacokinetic (PK) profile (levels, persistence, trafficking) of CTL019 cells in target tissues (blood, bone marrow, CSF, and other tissues if available)	• CTL019 transgene levels by qPCR in blood, bone marrow and CSF if available • Expression of CTL019 detected by flow cytometry in blood and bone marrow • Cmax, Tmax, AUCs and other relevant PK parameters of CTL019 in blood, bone-marrow, CSF if available • Persistence of CTL019 in blood, bone marrow, and CSF if available (eg Mean Residence Time [MRT] last)	Refer to Section 10.5.4.
Describe the prevalence and incidence of immunogenicity to CTL019	• Prevalence and incidence of immunogenicity and anti-CTL019 assay titers	Refer to Section 10.5.3.4.
Describe the effect of CTL019 therapy on Patient Reported Outcomes (PRO)	• PRO as measured by PedsQL and EQ-5D questionnaires	Refer to Section 10.5.2.7

[redacted]

Objective	Endpoint	Analysis
Derivation of a score to predict cytokine release syndrome	• Develop a score utilizing clinical and biomarker data and assess its ability for early prediction of cytokine release syndrome	Refer to Section 10.5.3.5
Describe the profile of soluble immune factors that may be key to cytokine release syndrome	• Frequent monitoring of concentrations of soluble immune factors in blood	Refer to Section 10.5.3.6
Describe the levels of B and T cells (peripheral blood and bone marrow) prior to and following CTL019 infusion for safety monitoring	• Lymphocyte subsets of B and T cells and description of associated safety events	Refer to Section 10.5.3.7
Assess the efficacy, safety and in vivo cellular pharmacokinetics of patients infused with CTL019 manufactured by [redacted]	• ORR and MRD negative remission • Type, frequency and severity of adverse events and laboratory abnormalities • CTL019 transgene levels by qPCR in blood, bone marrow and CSF if available	Refer to Section 10.5.2.11 Not applicable at Interim analysis
Exploratory		
Determine the incidence and pattern of tumor clonal evolution	• [redacted]	Refer to Section 10.6.
T cell trafficking (CTL019 immunophenotyping)	• CTL019 positive T cells and other leukocyte subsets	Refer to Section 10.6.
Describe the effect of anti-cytokine therapy on CRS, CTL019 PK/PD, and tumor response	• Clinical CRS adverse events and laboratory measures of CRS (e.g. IL-6, C-reactive protein (CRP) and ferritin concentrations) by anti-cytokine therapy • CTL019 concentrations by anti-cytokine therapy • Disease response by anti-cytokine therapy	Refer to Section 10.6.
Quantify the relationship between 1) CTL019 cell product/leukapheresis product [redacted] 2) other cell product/leukapheresis product characteristics and clinical endpoints (efficacy, safety, PK)	• [redacted] • Leukapheresis and cell product characteristics [redacted] • Clinical response (CR, CRi, relapse) • MRD and B cell recovery assay results • PK parameters • CRS status • Cytokine response	Refer to Section 10.6.

[redacted]

Objective	Endpoint	Analysis
To explore the relationships between CRS, initial tumor burden, clinical tumor response, and PK/PD parameters	• CRS occurrence, CRS grade, need for anti-cytokine therapies • Baseline tumor burden • Clinical tumor response at Day 28 • CTL019 concentrations and B cell depletion	Refer to Section 10.6.
[redacted]	• [redacted]	Refer to Section 10.6.
To describe hospital resource utilization	• Number of patients with hospitalized infusion, total number of hospitalizations, and length of stay	Refer to Section 10.6.

[redacted]

4 Study design

4.1 Description of study design

This is a single arm, multi-center, phase II study to determine the efficacy and safety of CTL019 in pediatric patients with relapsed or refractory B-cell ALL. The study will have the following sequential phases for all patients: Screening (Section 7.1.1), Pre-Treatment (Cell Product Preparation and Lymphodepleting Chemotherapy; Section 7.1.2), Treatment and Primary Follow-up (Section 7.1.3), Secondary Follow-up (if applicable, Section 7.1.4), and Survival Follow-up (Section 7.1.5). The total duration of the study is 5 years. After CTL019 infusion, efficacy will be assessed monthly for the first 6 months, then quarterly up to 2 years and semi-annually afterwards up to 5 years, or until patient relapse. Efficacy assessments will be based on the Novartis guidelines for response assessment in ALL (Appendix 1), which is based on NCCN version 1.2013 guidelines, Cheson et al (2003) and Appelbaum et al (2007). Safety will be assessed throughout the study. A post-study long term follow-up (Section 7.1.6) for lentiviral vector safety will continue under a separate destination protocol per the following health authority guidelines: FDA (2006a), FDA (2006b), European Medicines Agency (EMA) (2008) and EMA (2009).

At the beginning of the trial, a **safety run-in stage** will be conducted to enroll three patients for the purpose of assessing the acute safety profile of the Novartis CTL019 cell product. The acute and subacute toxicity profile for CTL019 cell product manufactured at the University of Pennsylvania has been established in patients with r/r B-cell ALL. This data demonstrates that the majority of tumor lysis syndrome, cytokine release syndrome and chemotherapy toxicities have manifested within the first two weeks post-CTL019 infusion in r/r ALL patients. The first three patients will be enrolled in a staggered manner (waiting 14 days prior to treating the next patient) for the purpose of assessing the acute and subacute safety profile. Safety profiles during the first 14 days post infusion will be reported to the Health Authorities.

The data to be reported will include demographics, lymphodepleting chemotherapy, total and CTL019 transduced viable T cell doses, AE/ Serious Adverse Events (SAEs), standard laboratory data (hematology and chemistry) and CTL019 cellular PK.

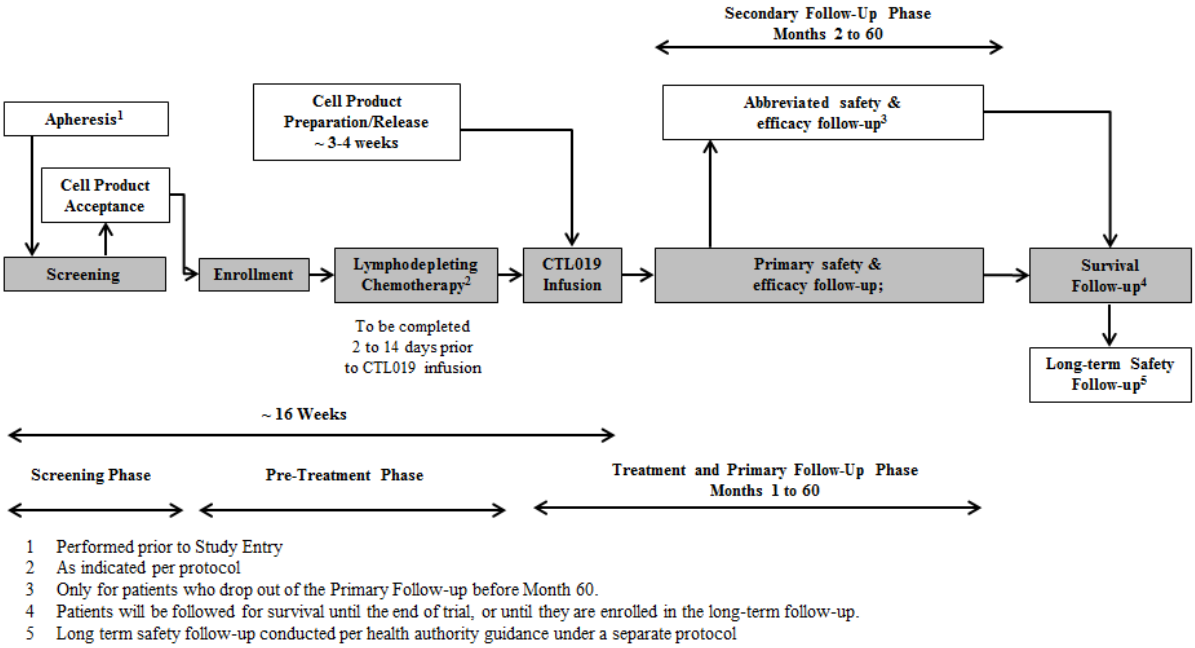
For the purpose of safety onboarding of new sites, after the above safety run-in stage has been completed, a staggered approach will also be utilized at each new respective site (with no prior experience administering CTL019) and will occur as follows:

- 1st patient enrollment, wait 14 days
- 2nd patient enrollment, wait 14 days
- Following completion of this staggered enrollment of the first two patients, the new site may then proceed with enrollment of patients without the stagger.

Initially, manufacturing of CTL019 has been performed at the Novartis Morris Plains manufacturing facility and will be expanded to the [redacted] to establish a CTL019 manufacturing site in Europe. Approximately 14 patients will be enrolled in Region Europe to allow at least 10 patients infused with CTL019 manufactured at the [redacted]

[redacted]

Figure 4-1 Study design



1 Performed prior to Study Entry
2 As indicated per protocol
3 Only for patients who drop out of the Primary Follow-up before Month 60.
4 Patients will be followed for survival until the end of trial, or until they are enrolled in the long-term follow-up.
5 Long term safety follow-up conducted per health authority guidance under a separate protocol

4.1.1 Leukapheresis assessment

Cryopreserved non-mobilized leukapheresis products collected from the patient prior to study entry (historical) may be usable for CTL019 manufacturing if collected at an appropriately certified apheresis center and the product is accepted by the manufacturing facility. If a historical leukapheresis product is not available, an apheresis procedure will be scheduled for cell procurement via institutional leukapheresis protocols/procedures or the Novartis leukapheresis protocol ([CTL019B2206]). It is strongly recommended that apheresis be scheduled prior to any planned administration of chemotherapy, immunomodulators, or non-physiologic dose of steroids to ensure an adequate absolute lymphocyte count (ALC). Ideally, patients should have [redacted] for leukapheresis collection. However, patients with an [redacted] during leukapheresis screening should have a CD3 (T-cells) cell count of [redacted] to be eligible for leukapheresis collection.

Sample sentinel vials collected from the leukapheresis product will be sent to Novartis designated manufacturing facility prior to or with shipment of the leukapheresis product.

For guidelines on optimal patient timing of leukapheresis collection, cell number requirements, and concomitant medication restrictions, please refer to the Leukapheresis Key Requirements within the [Leukapheresis, Cryopreservation & Scheduling Manual].

Patients may be consented for the Novartis leukapheresis protocol (CTL019B2206) prior to or after consent has been obtained for the CTL019 treatment protocol dependent upon local requirements.

For patients developing grade 2 to 4 acute GVHD or extensive chronic GVHD following the collection of a leukapheresis product, such a leukapheresis product cannot be used for

[redacted]

CTL019 manufacturing or infusion due to concerns of auto-reactive T cells with an increased risk for inducing or exacerbating GVHD by the manufactured product.

During the screening phase, informed consent/assent will be signed and all clinical eligibility criteria (defined as all inclusion/exclusion criteria except that which pertains to the leukapheresis product) will be assessed. Only following informed consent/assent and confirmation of all clinical eligibility criteria will the patient's leukapheresis product and sentinel vial(s), as requested by the manufacturing facility, be shipped to the manufacturing facility. The manufacturing facility will then evaluate the patient's leukapheresis product for acceptance. Enrollment is defined as the point at which the patient meets all clinical inclusion/exclusion criteria, and the patients' leukapheresis product is received and accepted by the manufacturing facility.

[redacted]

4.2 Definition of end of the study

The end of study is defined as the last patient's last visit (LPLV), which is the last patient's Month 60 evaluation, or the time of premature withdrawal.

Patients who discontinue the "Treatment and Primary Follow-Up Phase" before month 60 will continue to be followed in the secondary follow-up phase in order to collect health authority requested data (e.g. delayed adverse events) up to 5 years after CTL019 infusion. It is anticipated that patients may leave the primary follow-up and move to secondary follow-up due to reasons including: treatment failure, relapse after remission, pursuing SCT while in remission, or withdrawal from the primary follow-up.

In addition, semiannual and annual evaluations will be performed for up to 15 years on all patients under a separate destination protocol as recommended by health authority guidance for patients treated with gene therapies. All patients who either complete the study or prematurely discontinue from the study will be enrolled in this destination protocol at the time of study completion/discontinuation (separate informed consent/assent forms will be provided for this protocol; Section 7.1.6).

Patients may continue to be followed under the current protocol for survival until end of study as defined above or until they choose to enroll into the long term follow-up protocol ([CCTL019A2205B]), whichever occurs first. The survival follow-ups can be conducted via the form of telephone contact.

4.3 Early study termination

The study can be terminated at any time for any reason by the sponsor, Novartis, or if any of the stopping criteria described in Section 6.2.4.1.1 are met. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. For patients who have received a CTL019 infusion, a long term post-study follow-up for lentiviral vector safety will still continue under a separate destination protocol for 15 years post infusion per health authority guidelines. The

[redacted]

investigator will be responsible for informing Institutional Review Boards (IRBs) and/or Independent Ethics Committees (IECs) of the early termination of the trial.

5 Population

5.1 Patient population

The target population consists of pediatric patients with B-cell ALL who are chemo-refractory, relapsed after allogeneic SCT, or are otherwise ineligible for allogeneic SCT. Approximately 95 patients will be enrolled between the age of 3 years at the time of screening to the age of 21 years at the time of initial diagnosis. This will include at least 50 infused patients less than the age of 18 at the time of screening, at least 10 of which will be under the age of 10. Patients 18 years of age or older at screening will be limited to 10 total infused patients. When 10 patients ≥ 18 years of age have been infused, further enrollment in this age category will require Sponsor approval. Approximately 14 patients will be enrolled to ensure at least 10 patients are infused with CTL019 manufactured by the [redacted]. The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study must meet **all** of the following criteria:

1. Relapsed or refractory pediatric B-cell ALL
   a. 2nd or greater BM relapse OR
   b. Any BM relapse after allogeneic SCT and must be ≥ 6 months from SCT at the time of CTL019 infusion OR
   c. Primary refractory as defined by not achieving a CR after 2 cycles of a standard chemotherapy regimen or chemorefractory as defined by not achieving a CR after 1 cycle of standard chemotherapy for relapsed leukemia OR
   d. Patients with Ph+ ALL are eligible if they are intolerant to or have failed two lines of TKI therapy, or if TKI therapy is contraindicated OR
   e. Ineligible for allogeneic SCT because of:
      - Comorbid disease
      - Other contraindications to allogeneic SCT conditioning regimen
      - Lack of suitable donor
      - Prior SCT
      - Declines allogeneic SCT as a therapeutic option after documented discussion about the role of SCT with a BMT physician not part of the study team
2. For relapsed patients, CD19 tumor expression demonstrated in bone marrow or peripheral blood by flow cytometry within 3 months of study entry
3. Adequate organ function defined as:
   a. Renal function defined as:
      - A serum creatinine based on age/gender as follows:

[redacted]

	Maximum Serum Creatinine (mg/dL)	
Age	**Male**	**Female**
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1.0	1.0
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

   b. ALT ≤ 5 times the ULN for age
   c. Bilirubin < 2.0 mg/dl
   d. Must have a minimum level of pulmonary reserve defined as ≤ Grade 1 dyspnea and pulse oxygenation > 91% on room air
   e. LVSF ≥ 28% confirmed by echocardiogram, or LVEF ≥ 45% confirmed by echocardiogram or MUGA within 7 days of screening
4. Bone marrow with ≥ 5% lymphoblasts by morphologic assessment at screening
5. Life expectancy > 12 weeks
6. Age 3 years at the time of screening to age 21 years at the time of initial diagnosis
7. Karnofsky (age ≥16 years) or Lansky (age < 16 years) performance status ≥ 50 at screening
8. Signed written informed consent and assent forms if applicable must be obtained prior to any study procedures
9. Must meet the institutional criteria to undergo leukapheresis or have an acceptable, stored leukapheresis product
10. Once all other eligibility criteria are confirmed, must have a leukapheresis product of non-mobilized cells received and accepted by the manufacturing site. Note: Leukapheresis product will not be shipped to or assessed for acceptance by the manufacturing site until documented confirmation of all other eligibility criteria is received

5.3 Exclusion criteria

Patients meeting any of the following criteria must be excluded from the study:

1. Isolated extra-medullary disease relapse
2. Patients with concomitant genetic syndromes associated with bone marrow failure states: such as patients with Fanconi anemia, Kostmann syndrome, Shwachman syndrome or any other known bone marrow failure syndrome. Patients with Down Syndrome will not be excluded.
3. Patients with Burkitt's lymphoma/leukemia (i.e. patients with mature B-cell ALL, leukemia with B-cell [sIg positive and kappa or lambda restricted positivity] ALL, with FAB L3 morphology and /or a MYC translocation)
4. Prior malignancy, except carcinoma *in situ* of the skin or cervix treated with curative intent and with no evidence of active disease
5. Treatment with any prior gene therapy product

[redacted]

6. Has had treatment with any prior anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy
7. Active or latent hepatitis B or active hepatitis C (test within 8 weeks of screening), or any uncontrolled infection at screening
8. Human Immunodeficiency Virus (HIV) positive test within 8 weeks of screening
9. Presence of grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD)
10. [Retired from Amended Protocol Version 01]
11. Active CNS involvement by malignancy, defined as CNS-3 per NCCN guidelines. Note: Patients with history of CNS disease that has been effectively treated will be eligible
12. Patient has an investigational medicinal product within the last 30 days prior to screening
13. Pregnant or nursing (lactating) women. NOTE: female study participants of reproductive potential must have a negative serum or urine pregnancy test performed within 48 hours before infusion
14. [Retired from Amended Protocol Version 02]
15. [Retired from Amended Protocol Version 02]
16. Women of child-bearing potential (defined as all women physiologically capable of becoming pregnant) and all male participants, unless they are using highly effective methods of contraception for a period of 1 year after the CTL019 infusion. Highly effective contraception methods include:
    a. Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are NOT acceptable methods of contraception
    b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    c. Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
    d. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
    e. Use of IUDs are excluded due to increased risks of infection and bleeding in this population. However, IUD inserted prior to consent may remain in place, and a second method of contraception is mandated.
    f. In case of use of oral contraception, women must be stable on the same pill for a minimum of 3 months before taking study treatment

    Women who are not of reproductive potential (defined as either <11 years of age, Tanner Stage 1, post-menopausal for at least 24 consecutive months (i.e. have had no menses) or have undergone hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy) are eligible without requiring the use of contraception. Women who are not yet of reproductive potential are to agree to use acceptable forms of contraception when they reach reproductive potential if within 1 year of CTL019 or if CAR cells are present in the

[redacted]

blood by PCR. Acceptable documentation includes written or oral documentation communicated by clinician or clinician's staff of one of the following:

a. Demographics show age <11
b. Physical examination indicates Tanner Stage 1
c. Physician report/letter
d. Operative report or other source documentation in the patient record
e. Discharge summary
f. Follicle stimulating hormone measurement elevated into the menopausal range

17. The following medications are excluded:

a. **Steroids:** Therapeutic systemic doses of steroids must be stopped > 72 hours prior to CTL019 infusion. However, the following physiological replacement doses of steroids are allowed: < 12 mg/m^2/day hydrocortisone or equivalent
b. **Allogeneic cellular therapy:** Any donor lymphocyte infusions (DLI) must be completed > 6 weeks prior to CTL019 infusion
c. **GVHD therapies:** Any systemic drug used for GVHD must be stopped > 4 weeks prior to CTL019 infusion to confirm that GVHD recurrence is not observed (e.g. calcineurin inhibitors, methotrexate or other chemotherapy drugs, mycophenolyate, rapamycin, thalidomide, or immunosuppressive antibodies such as anti-CD20 (rituximab), anti-TNF, anti-IL6 or anti-IL6R, systemic steroids)
d. **Chemotherapy:**
   - Tyrosine kinase inhibitors and hydroxyurea must be stopped > 72 hours prior to CTL019 infusion
   - The following drugs must be stopped > 1 week prior to CTL019 infusion and should not be administered concomitantly or following lymphodepleting chemotherapy: vincristine, 6-mercaptopurine, 6-thioguanine, methotrexate < 25 mg/m^2, cytosine arabinoside < 100 mg/m^2/day, asparaginase (non-pegylated)
   - The following drugs must be stopped >2 weeks prior to CTL019 infusion: salvage chemotherapy (e.g. clofarabine, cytosine arabinoside > 100 mg/m^2, anthracyclines, cyclophosphamide, methotrexate ≥ 25 mg/m^2), excluding the required lymphodepleting chemotherapy drugs
   - Pegylated-asparaginase must be stopped > 4 weeks prior to CTL019 infusion
e. **CNS disease prophylaxis:** CNS prophylaxis treatment must be stopped > 1 week prior to CTL019 infusion (e.g. intrathecal methotrexate)
f. **Radiotherapy**
   - Non-CNS site of radiation must be completed > 2 weeks prior to CTL019 infusion
   - CNS directed radiation must be completed > 8 weeks prior to CTL019 infusion
g. **Anti T-cell Antibodies:** Administration of any T cell lytic or toxic antibody (e.g. alemtuzumab) within 8 weeks prior to CTL019 is prohibited since residual lytic levels may destroy the infused CTL019 cells and/or prevent their in vivo expansion. If such an agent has been administered within 8 weeks prior to CTL019, contact the Sponsor,

[redacted]

consider consultation with an pharmacology expert, and consider measuring residual drug levels, if feasible, prior to CTL019 infusion.

6 Treatment

6.1 Study treatment

CTL019 is an autologous cellular immunotherapy product that is comprised of CD3+ T cells that have undergone *ex vivo* T cell activation, gene modification, expansion and formulation in infusible cryomedia. The transgene to be expressed via lentiviral vector transduction is a CAR targeted against the CD19 antigen. The CAR contains a murine scFv that targets CD19 linked to a transmembrane region derived from the CD8 receptor, which is linked to an intracellular bipartite signaling chain of TCR-ζ (or CD3-ζ) and 4-1BB intracellular signaling domains. The extracellular scFv with specificity for CD19 is derived from a mouse monoclonal antibody. T cells which are enriched from a patient leukapheresis unit are expanded *ex vivo* using commercially available magnetic beads that are coated with anti-CD3 and anti-CD28 monoclonal antibodies. The cells are transduced with the CD19 CAR lentiviral vector which ensures that only peripheral white blood cells enriched for lymphocytes are exposed to the vector. The residual non-integrated vector is washed away during the process. CTL019 cells expand *ex vivo* for approximately 10 days. At the end of the culture, the CTL019 cells are depleted of magnetic beads, washed, concentrated, and cryopreserved. Results from a release testing procedure are required prior to release of the product for infusion.

A target per-protocol dose of CTL019 transduced cells for pediatric patients will consist of a single infusion of 2.0 to 5.0 x 10^6 CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 1.0 to 2.5 x 10^8 CTL019 transduced viable T cells (for patients > 50 kg). The following cell dose ranges may be infused if all other safety release criteria are met: 0.2 to 5.0 x 10^6 CTL019 transduced viable T cells per kg body weight (for patient ≤ 50 kg) and 0.1 to 2.5 x 10^8 CTL019 transduced viable T cells (for patients > 50 kg).

6.1.1 Dosing regimen

6.1.1.1 Lymphodepleting chemotherapy

It is anticipated that many patients will have been receiving chemotherapy for relapse or resistant disease. Prior to CTL019 cell infusion, an additional lymphodepleting chemotherapy cycle is planned. The use of any additional chemotherapy prior to the recommended preinfusion, lymphodepleting chemotherapy will be at the discretion of the investigator and dependent on the patient's disease burden.

When given, lymphodepleting chemotherapy should be started before CTL019 infusion so that CTL019 cells will be given 2 to 14 days after completion of the lymphodepleting chemotherapy. The chemotherapy start date will vary based on the selected chemotherapy. The purpose of this chemotherapy is to induce lymphopenia in order to facilitate engraftment and homeostatic expansion of CTL019 cells. For lymphodepleting chemotherapy, cyclophosphamide-based regimens are the agents of choice as there is the most experience

[redacted]

with the use of these agents in facilitating adoptive immunotherapy. The lymphodepleting regimen is:

- Fludarabine (30 mg/m^2 intravenously [i.v.] daily for 4 doses) and cyclophosphamide (500 mg/m^2 i.v. daily for 2 doses starting with the first dose of fludarabine)

If there was previous Grade 4 hemorrhagic cystitis with cyclophosphamide, or the patient demonstrated a chemorefractory state to a cyclophosphamide-containing regimen administered shortly before lymphodepleting chemotherapy, then the following will be used:

- Cytarabine (500 mg/m^2 i.v. daily for 2 days) and etoposide (150 mg/m^2 i.v. daily x 3 days starting with the first dose of cytarabine)

If patients have a White Blood Cell (WBC) count ≤ 1,000 cells/μL within one week prior to CTL019 infusion, lymphodepleting chemotherapy is **NOT** required.

6.1.1.2 CTL019 infusion

The CTL019 cell product will be released to the study site approximately 3 to 4 weeks after manufacturing has commenced, provided all required safety and quality release criteria have been met.

Prior to CTL019 infusion: the following criteria must be met:

1. **Influenza Testing:** All patients must undergo a rapid influenza diagnostic test within 10 days prior to the planned CTL019 infusion. If the patient is positive for influenza, he/she should complete a full course of oseltamivir phosphate or zanamivir as described in the label (see Tamiflu® or Relenza® package insert for dosing). The patient must complete their full course of treatment **prior** to receiving CTL019. The test does not need to be repeated prior to CTL019 infusion however if flu-like or respiratory signs and symptoms are present, CTL019 infusion should be delayed until the patient is asymptomatic. For patients residing in the United States, Canada, Europe, and Japan, influenza testing is required during the months of October through May, inclusive. For patients residing in the Southern Hemisphere such as Australia, influenza testing is required during the months of April through November, inclusive. For patients with significant international travel, both calendar intervals may need to be considered.
2. **Performance Status:** Patient should not experience a significant change in clinical or performance status compared to initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of adverse events associated with experimental cell infusion.
3. **Laboratory Abnormalities:** Patients experiencing laboratory abnormalities after enrollment, that in the opinion of the treating investigator or PI may impact subject safety or the subjects' ability to receive the CTL019 infusion, may have their infusion delayed until it is determined to be clinically appropriate to proceed with the CTL019 infusion.
4. **Leukemia Disease Status:** Prior to CTL019 infusion and following lymphodepleting (LD) chemotherapy, patients must not have accelerating disease, as this will put them at unacceptable risk for severe CRS. Patients should not receive CTL019 infusion if they exhibit significant progression of disease during or following LD chemotherapy as evidenced by
    - Significant and increasing circulating blasts

[redacted]

- Significant increases in organomegaly
- Clinical evidence of new CNS disease

5. **Chemotherapy Toxicity:** Patients experiencing toxicities from their preceding lymphodepleting chemotherapy will have their infusion schedule delayed until these toxicities have been resolved (to grade 1 or baseline). The specific toxicities warranting delay of CTL019 cell infusion include:
   a. **Pulmonary:** Requirement for supplemental oxygen to keep saturation greater than 91% or presence of progressive radiographic abnormalities on chest x-ray
   b. **Cardiac:** New cardiac arrhythmia not controlled with medical management. Pre-infusion ECG also required (Table 7-1).
   c. **Hypotension:** requiring vasopressor support
6. **Infection:** CTL019 infusion must be delayed if there is an uncontrolled active infection, as evidenced by positive blood cultures for bacteria, fungus, or PCR positivity for viral DNA within 72 hours of CTL019 cell infusion, or clinical or radiographic evidence of active infection. Following the treatment of a recent infection, significant improvement must be established either clinically and/or radiographically, prior to CTL019 infusion
7. **GVHD Status:** Patients should not be infused if they develop grade 2-4 acute or extensive chronic GVHD since the time of screening.
8. **Concomitant Medications:** If patients are taking any of the following medications, their infusion must be delayed until the medications have been stopped according to the following:
   a. **Steroids:** Therapeutic systemic doses of steroids must be stopped > 72 hours prior to CTL019 infusion. However, the following physiological replacement doses of steroids are allowed: < 12 mg/m^2/day hydrocortisone or equivalent
   b. **Allogeneic cellular therapy:** Any donor lymphocyte infusions (DLI) must be completed > 6 weeks prior to CTL019 infusion
   c. **GVHD therapies:** Any systemic drug used for GVHD must be stopped > 4 weeks prior to CTL019 infusion to confirm that GVHD recurrence is not observed (e.g. calcineurin inhibitors, methotrexate or other chemotherapy drugs, mycophenolyate, rapamycin, thalidomide, or immunosuppressive antibodies such as rituximab, anti-TNF, anti-IL6 or anti-IL6R, systemic steroids)
   d. **Chemotherapy:**
      - Tyrosine kinase inhibitors and hydroxyurea must be stopped > 72 hours prior to CTL019 infusion
      - The following drugs must be stopped > 1 week prior to CTL019 infusion and should not be administered concomitantly or following lymphodepleting chemotherapy: vincristine, 6-mercaptopurine, 6-thioguanine, methotrexate < 25 mg/m^2, cytosine arabinoside < 100 mg/m^2/day, asparaginase (non-pegylated)
      - The following drugs must be stopped > 2 weeks prior to CTL019 infusion: salvage chemotherapy (e.g. clofarabine, cytosine arabinoside > 100 mg/m^2, anthracyclines, cyclophosphamide, methotrexate ≥ 25 mg/m^2), excluding the required lymphodepleting chemotherapy drugs
      - Pegylated-asparaginase must be stopped > 4 weeks prior to CTL019 infusion

[redacted]

e. **CNS disease prophylaxis:**
   - CNS prophylaxis treatment must be stopped > 1 week prior to CTL019 infusion (e.g. intrathecal methotrexate)

f. **Radiotherapy**
   - Non-CNS site of radiation must be completed > 2 weeks prior to CTL019 infusion
   - CNS directed radiation must be completed > 8 weeks prior to CTL019 infusion

g. **Anti T-cell Antibodies:** Administration of any T cell lytic or toxic antibody (e.g. alemtuzumab) within 8 weeks prior to CTL019 is prohibited since residual lytic levels may destroy the infused CTL019 cells and/or prevent their in vivo expansion. If such an agent has been administered within 8 weeks prior to CTL019, contact the Sponsor, consider consultation with a pharmacology expert, and consider measuring residual drug levels, if feasible, prior to CTL019 infusion.

9. **Stem Cell Transplant:** Reconfirm that patient is ≥ 6 months from SCT at the time of CTL019 infusion (if applicable)
10. **Lymphodepleting Chemotherapy Timing:** If a delay is **4 or more weeks** from completing lymphodepleting chemotherapy and the WBC > 1000/μL, the patient will need to be re-treated with lymphodepleting chemotherapy.
11. **Cardiac Evaluations:** In the event that the time between screening cardiac ECHO/MUGA and CTL019 infusion exceeds 6 weeks, cardiac imaging must be repeated to confirm a LVSF ≥ 28 % by echocardiogram, or LVEF ≥ 45 % by echocardiogram or MUGA.
12. **Pregnancy:** Patient must undergo a pregnancy test (urine or serum) within 48 hours prior to infusion (Table 7-1).

Additional safety procedures prior to administration: The risk of tumor lysis syndrome (TLS) is dependent on disease burden. Patients will be closely monitored both before and after lymphodepleting chemotherapy and CTL019 infusions including blood tests for potassium and uric acid. Patients with elevated uric acid or high tumor burden will receive prophylactic allopurinol, or a non-allopurinol alternative (e.g. febuxostat). Infection prophylaxis should follow local guidelines dictated only by the preceding lymphodepleting chemotherapy. Infection prophylaxis *per se* for CTL019 is not recommended.

The site must confirm that two doses of tocilizumab are on site **prior to CTL019 infusion** and one dose of siltuximab must be accessible within 24 hours of infusion for administration in order to manage suspected toxicities.

Premedication: Side effects from T cell infusions can include fever, chills and/or nausea. All patients should be pre-medicated with acetaminophen or paracetamol and diphenhydramine or an H1 antihistamine. These medications can be repeated every 6 hours as needed. Non-steroidal anti-inflammatory medication may be prescribed if the patient continues to have fever not relieved with acetaminophen or paracetamol. Steroids should NOT be used for premedication. It is recommended that patients NOT receive systemic corticosteroids other than physiologic replacement of hydrocortisone at any time, except in the case of life threatening emergency, since this may have an adverse effect on CTL019 cell expansion and function.

[redacted]

Cell thawing and infusion of CTL019 product: A study physician MUST evaluate the patient just prior to infusion to ensure the patient meets CTL019 infusion criteria. Trained study staff will administer the CTL019 infusion using precautions for immunosuppressed patients. Protective isolation should follow institutional standards and policies. Emergency medical equipment should be available during the infusion in case the patient has a significant reaction to the infusion such as anaphylaxis or severe hypotension.

The CTL019 dose will be administered via a single intravenous infusion. Depending on the volume of the CTL019 product, it will be given either as an i.v. infusionthrough a latex free i.v. tubing WITHOUT a leukocyte filter (approximately 10 – 20 mL per minute adjusted as appropriate for smaller children and smaller volumes) or as an i.v. push via a syringe (for smaller volumes). It is recommended that the infusion/i.v. push be completed within 30 minutes of thawing the cryopreserved product in order to preserve maximum cell viability. Vital signs (temperature, respiration rate, pulse, pulse oximetry, and blood pressure) will be taken prior to, during and immediately after the infusion and then approximately every 15 minutes for one hour and repeated at 2 hours. If vital signs are unsatisfactory and unstable, continue to monitor the patient until vital sign stabilization.

All used infusion supplies, including the infusion bag and tubing, must be disposed of according to local institutional standard operating procedures. For further details on product storage, preparation, thawing and administration, please refer to the specific guidance provided in the [Investigational Product Handling Manual].

Following CTL019 infusion: Should emergency treatment be required in the event of life-threatening hypersensitivity or other acute infusion-related reaction, supportive therapy such as oxygen, bronchodilators, epinephrine, antihistamines, and corticosteroids should be given according to local institutional guidelines. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Patient or patient's caregiver should monitor the patient's temperature twice a day for the first 14 days. The patient or patient's caregiver should be instructed to call the investigator promptly with any signs of fever for possible hospitalization.

Supportive care: Local guidelines will be followed for the supportive care of immunosuppressed and chemotherapy treated patients including infection management. All blood products administered should be irradiated. Immunosuppressive medications, including steroids, should not be administered unless life threatening circumstances arise.

6.1.2 Ancillary treatments

As side effects from T cell infusions can include fever, chills and/or nausea, all patients should be pre-medicated with acetaminophen or paracetamol and diphenhydramine or an H1 antihistamine, as described above in Section 6.1.1.2. If fever develops please follow your institutional guidelines for patients with fever/neutropenia and strongly consider admission for close observation.

6.1.3 Treatment for cytokine release syndrome

Management of CRS following CTL019 administration must follow the CRS treatment algorithm in Figure 6-1. CTL019 administration may require tocilizumab (recommended label

[redacted]

dose 8 mg/kg for patients weighing ≥ 30 kg and 12 mg/kg for patients weighing < 30 kg; IV infusion over 1 hour), steroids, and siltuximab (11 mg/kg IV over 1 hour) for the treatment of suspected CRS toxicities as described below in Section 6.2.4.2. The site must confirm that two doses of tocilizumab are on site and available for administration **prior to CTL019 infusion** and one dose of siltuximab must be accessible **within 24 hours of infusion**. All other medications (except for tocilizumab or siltuximab administration), including steroids given to treat CRS, must be listed on the concomitant medication CRF. Tocilizumab or siltuximab should be reported on the "Dosage Administration Record - Tocilizumab" or "Dosage Administration Record - Siltuximab" eCRF, respectively.

6.1.4 Guidelines for continuation of treatment

Not applicable.

6.1.5 Treatment duration

A single dose of CTL019 transduced viable T cells will be given.

6.2 Dose escalation guidelines

Not applicable.

6.2.1 Starting dose rationale

Not applicable.

6.2.2 Provisional dose levels

Not applicable.

6.2.3 Guidelines for dose escalation and determination of MTD/RP2D/RDE

Not applicable.

6.2.3.1 Implementation of dose escalation decisions

Not applicable.

6.2.3.2 Intra-patient dose escalation

Not applicable.

6.2.4 Definitions of dose limiting toxicities (DLTs) in a Phase II Study

There are no dose-limiting toxicities in this protocol; however criteria for stopping or pausing the trial are detailed below.

6.2.4.1 Toxicity management, stopping rules and study termination

It is expected that AEs will occur frequently in this population based on the underlying advanced hematologic malignancy and that these can be SAEs. Therefore, there is no specific occurrence of SAEs that define a stopping rule, but the review of SAEs will form the basis for

[redacted]

potential early stopping of the study. Only unexpected SAEs that are related to the CTL019 transduced cells would define a stopping rule. The review of these adverse events, and any decision to prematurely stop patient enrollment, will be determined by the Data Monitoring Committee (DMC) and reviewed by the IRB at the site level.

Premature termination of the clinical trial may occur because of a regulatory authority decision, the DMC, or determination that there are problems in the cell product generation or safety at the discretion of the study investigators. Additionally, recruitment may be stopped at the sponsor's discretion and may include reasons such as low recruitment, protocol violations, or inadequate data recording.

6.2.4.1.1 Criteria for stopping or pausing the study

During the **safety run-in stage** the study will be paused, and health authorities notified, if at least one of the following events occur:

- Life-threatening (grade 4) toxicity attributable to protocol therapy that is unmanageable, unexpected and unrelated to chemotherapy and attributable to CTL019 therapy. High fevers, hypotension, hypoxia, disseminated intravascular coagulation, encephalopathy (e.g. lethargy, confusion, aphasia, seizures), intensive care unit (ICU) admission, dialysis and mechanical ventilation are expected. The expected side effects can also result in grade 4 liver toxicity, nephrotoxicity and other organ involvement
- Death suspected to be related to CTL019 therapy

Beyond the **safety run-in stage**, the overall study will be paused, and health authorities notified if:

- Any patient develops uncontrolled T cell proliferation beyond 8 weeks from CTL019 cell product infusion that does not respond to management
- Any patient develops detectable replication competent lentivirus (RCL) during the study
- The Sponsor, DMC, or any regulatory body decides for any reason that patient safety may be compromised by continuing the study
- The Sponsor decides to discontinue the development of the intervention to be used in this study

The study may be paused pending notification of the health authorities and the DMC for investigation and possible protocol amendment if any patient experiences any of the following events within three weeks of the CTL019 cell infusion:

- Life-threatening (grade 4) toxicity attributable to protocol therapy that is unmanageable, unexpected and unrelated to chemotherapy and attributable to protocol therapy. High fevers, hypotension, hypoxia, disseminated intravascular coagulation, encephalopathy (e.g. lethargy, confusion, aphasia, seizures), ICU admission, dialysis and mechanical ventilation are expected. The expected side effects can also result in grade 4 liver toxicity, nephrotoxicity and other organ involvement
- Death suspected to be related to CTL019 therapy

[redacted]

6.2.4.2 General toxicity management considerations

Acute infusion reaction

Acetaminophen/paracetamol and diphenhydramine/H1 antihistamine may be repeated every 6 hours as needed. A course of non-steroidal anti-inflammatory medication may be prescribed if the patient continues to have fever not relieved by acetaminophen/paracetamol. It is recommended that patients not receive corticosteroids at any time, except those already on physiologic replacement therapy, or in the case of a life threatening emergency, since this may have an adverse effect on CTL019 cells.

Febrile reaction

In the event of febrile reaction, an evaluation for infection should be initiated, and patients managed appropriately with antibiotics, fluids and other supportive care as medically indicated and determined by the treating physician. Inpatient treatment is recommended initially. In the event that the patient develops sepsis or systemic bacteremia following CTL019 cell infusion, appropriate cultures and medical management should be initiated. If a contaminated CTL019 cell product is suspected, the product can be retested for sterility using archived samples that are stored at the manufacturing site. Consideration of a cytokine release syndrome (see below) should be given.

Cytokine release syndrome (CRS) / macrophage activation syndrome (MAS)

Data from CTL019 treated patients experiencing CRS show marked elevations in IL6 and IFN-g. The symptoms generally occur 1-14 days after cell infusion in patients with ALL and may include high fevers, rigors, myalgia/arthralgias, nausea/vomiting/anorexia, fatigue, headache, encephalopathy, hypotension, dyspnea, tachypnea and hypoxia. Renal failure/renal injury, hyperbilirubinemia and increased ALT or AST can also occur. Supportive care and anti-cytokine therapy have been used for effective management of CRS. Prompt responses to tocilizumab have been seen in most patients Several patients with a suboptimal response to the first dose of tocilizumab have received a second or third dose of tocilizumab with CRS resolution. In patients with incomplete resolution of CRS after several doses of tocilizumab, CRS resolution has been observed following siltuximab administration. If the patient experiences ongoing CRS despite administration of repeated anti-cytokine directed therapies with tocilizumab, steroids and siltuximab, anti-T-cell therapies such as cyclophosphamide, anti-thymocyte globulin (ATG) or alemtuzumab may be considered and need to be captured in case report forms. Fatal outcomes associated with CRS have been observed in adult ALL patients in the context of current significant clinical infections.

A detailed treatment algorithm has been established with clear criteria for CRS management and guidance on when to administer tocilizumab and siltuximab as presented below in Figure 6-1 and must be followed by investigators. Tumor necrosis factor (TNF alpha) antagonists have been used with CTL019 associated CRS with little evidence for efficacy. Given the apparent lack of activity combined with their immunosuppressive effects, TNF antagonists are not recommended. This approach was designed to avoid life-threatening toxicities, while attempting to allow the CTL019 transduced cells to establish a proliferative phase which

[redacted]

appears to correlate with tumor response. Patients will be required to remain proximal to the treating site for the first 21 days.

The management of CRS is based solely upon clinical parameters as described in Figure 6-1 below. Serum cytokine and inflammatory marker levels should NOT be used for clinical management decisions of CRS.

Cases of transient left ventricular dysfunction, as assessed by cardiac ECHO, have been reported in some patients with severe CRS (grade 4). Therefore, consideration should be given to monitoring cardiac function by cardiac ECHO, during severe CRS, especially in cases with prolonged severe hemodynamic instability, delayed response to high dose vasopressors, and/or severe fluid overload.

Clinically significant coagulopathy is often seen with moderate to severe CRS (Grade 3 and 4) and may continue as CRS is beginning to clinically resolve. Coagulation parameters (PT, aPTT, and fibrinogen) should be more frequently monitored in this setting. CTL019 associated coagulopathy with or without clinical bleeding and hypofibrinogenemia is strongly recommended to be managed with cryoprecipitate or fibrinogen concentrate in addition to routine blood product support.

CTL019 related CRS can be associated with neurologic events. Two types of neurologic events with respect to timing of onset have been observed. Onset of neurologic events can be concurrent with high fevers during the development and maximal grade of CRS. Delayed onset of neurologic events can also occur as CRS is resolving or after CRS has completely resolved. Consideration should be given to monitoring for neurologic events during and after resolution of CRS.

A modification of the Common Terminology Criteria for Adverse Events (CTCAE) CRS grading scale has also been established to better reflect CTL019-therapy-associated CRS as presented in Table 6-1.

Specific CRFs have been developed for the capture of CRS elements, severity, management and response to intervention.

[redacted]

Figure 6-1 CRS management algorithm:

Pretreatment

Acetaminophen/paracetamol and diphenhydramine /H1 anti-histamine

Prophylaxis for complications of TLS as appropriate

CTL019 infusion

Prodromal syndrome: low grade fevers, fatigue, anorexia (hours to days)

Observation, rule out infection (surveillance cultures)

Antibiotics per local guidelines (febrile neutropenia)

Symptomatic support

Symptom progression: High fevers, hypoxia, mild hypotension

1st Line Management:

Oxygen, fluids, low dose vasopressor support, antipyretics

Monitor/manage complications of TLS

Further symptom progression:

- Hemodynamic instability despite intravenous fluids and moderate to "high dose" vasopressor[1] support OR
- Worsening respiratory distress, including pulmonary infiltrates increasing oxygen requirement including high-flow Oxygen (O2) and/or need for mechanical ventilation OR
- Rapid clinical deterioration

2nd Line Management:

Tocilizumab: IV infusion over 1 hour

- Patient weight < 30 kg: 12 mg/kg i.v.
- Patient weight ≥ 30 kg: 8 mg/kg i.v. (max dose 800 mg)

Hemodynamic and respiratory support

Lack of clinical improvement while awaiting tocilizumab response

3rd Line Management:

Consider other diagnosis causing clinical deterioration (i.e. sepsis, adrenal insufficiency)

If no improvement with 1st dose of tocilizumab within 12 to 18 hours, consider steroids (plan rapid taper **after** hemodynamic normalization):

2 mg/kg methylprednisolone as an initial dose, then 2 mg/kg per day. As steroids are tapered quickly, monitor for adrenal insufficiency and need for hydrocortisone replacement

If no response to steroids within 24 hours, consider 2nd dose of Tocilizumab (dosed as above)

Hemodynamic and respiratory support

Lack of clinical improvement while awaiting response to 3rd line management

4th Line Management:

Consider other diagnosis causing clinical deterioration (i.e. sepsis, adrenal insufficiency)

If no response to steroids and 2nd dose of tocilizumab within 24 hours or further clinical deterioration, consider siltuximab 11 mg/kg IV over 1 hour

Hemodynamic and respiratory support

Lack of clinical improvement while awaiting response to 4th line management

5th Line Management:

Consider other diagnosis causing clinical deterioration (i.e. sepsis, adrenal insufficiency)

In ongoing CRS despite prior therapy, consider anti-T cell therapies such as cyclophosphamide, anti-thymocyte globulin, or alemtuzumab

Hemodynamic and respiratory support

[1] See specific definition of "high dose" vasopressors in Table 6-2 below

[redacted]

Table 6-1 CTL019-therapy-associated grading for cytokine release syndrome: The Penn Grading Scale for Cytokine Release Syndrome (PGS-CRS)

1	2	3	4
Mild reaction: Treated with supportive care such as anti-pyretics and anti-emetics.	Moderate reaction: Requiring intravenous therapies or parenteral nutrition; some signs of organ dysfunction (i.e. grade 2 creatinine or grade 3 liver function tests [LFTs]) related to CRS and not attributable to any other condition. Hospitalization for management of CRS related symptoms including fevers with associated neutropenia.	More severe reaction: Hospitalization required for management of symptoms related to organ dysfunction including grade 4 LFTs or grade 3 creatinine related to CRS and not attributable to any other conditions; this excludes management of fever or myalgias. Includes hypotension treated with intravenous fluids* or low dose pressors, coagulopathy requiring fresh frozen plasma (FFP) or cryoprecipitate or fibrinogen concentrate, and hypoxia requiring supplemental oxygen (nasal cannula oxygen, high flow oxygen, Continuous Positive Airway Pressure [CPAP] or Bilateral Positive Airway Pressure [BiPAP]). Patients admitted for management of suspected infection due to fevers and/or neutropenia may have grade 2 CRS.	Life-threatening complications such as hypotension requiring high dose pressors (see Table 6-2) or hypoxia requiring mechanical ventilation.
• Marked elevations in IL-6, interferon gamma and less intensely TNF • Symptoms occur 1 to 14 days after cell infusion in ALL • Symptoms may include: High fevers, rigors, myalgia, arthralgia, nausea, vomiting, anorexia, fatigue, headache, hypotension, encephalopathy, dyspnea, tachypnea, and hypoxia • The start date of CRS is a retrospective assessment of the date of onset of persistent fevers and/or myalgia consistent with CRS and not explained by other events (i.e. sepsis). The stop date of CRS is defined as the date when the patient has been afebrile for 24 hours and off vasopressors for 24 hours			
*Defined as: multiple fluid boluses for blood pressure support			

Table 6-2 High dose vasopressor use

Definition of "High-Dose" Vasopressors	
Vasopressor	Dose for ≥ 3 hours
Norepinephrine monotherapy	≥ 0.2 mcg/kg/min
Dopamine monotherapy	≥ 10 mcg/kg/min
Phenylephrine monotherapy	≥ 200mcg/min
Epinephrine monotherapy	≥ 0.1 mcg/kg/min
If on vasopressin	High-dose if vaso + Norepinephrine Equivalent (NE) of ≥ 0.1 mcg/kg/min (using VASST formula)
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 20 mcg/min (using VASST formula)
VASST Trial Vasopressor Equivalent Equation: Norepinephrine equivalent dose = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min) ÷ 2] + [epinephrine (mcg/min)] + [phenylephrine (mcg/min) ÷10] Criteria from Russell et al (2008). **Note:** Pediatric weight adjustments should be taken into consideration	

[redacted]

Tumor lysis syndrome

Close monitoring for TLS before and after chemotherapy and CTL019 infusions, including blood tests (potassium, uric acid, etc.) will be done as follows:

- Screening phase:
  - Prophylactic allopurinol, or a non-allopurinol alternative (e.g. febuxostat), and increased oral/ IV hydration prior to lymphodepleting chemotherapy and CTL019 infusion should be given in patients with elevated uric acid or high tumor burden
  - Early and prompt implementation of supportive care in case of symptoms of acute TLS (i.v. hydration and rasburicase as clinically indicated, when uric acid continues to rise despite allopurinol/febuxostat and fluids)
- Post-infusion Monitoring phase:
  - Frequent monitoring of the following laboratory tests (2 to 3 times/week for 3 weeks from start of lymphodepleting chemotherapy, then weekly): potassium, phosphorus, calcium, creatinine, and uric acid
  - Encourage oral hydration

Laboratory and clinical TLS is defined as follows:

- Laboratory TLS is defined as two or more of the following values three days prior to or following CTL019 infusion.
  - Uric acid ≥ 8 mg/dL or 25% increase from baseline
  - Potassium ≥ 6 mEq/L or 25% increase from baseline
  - Phosphorus ≥ 6.5 mg/dL (children) or ≥ 4.5 mg/dL (adults) or 25% increase from baseline
  - Calcium ≤ 7 mg/dL or 25% decrease from baseline
  - If zero or one of the laboratory values above are abnormal, continue to manage with allopurinol or a non-allopurinol alternative (e.g. febuxostat) and oral hydration. Consider IV fluids and rasburicase if uric acid levels remain elevated, and consider in hospital monitoring
  - If Laboratory TLS exists, manage with i.v. fluids, laboratory blood tests every 6 to 8 hours and inpatient care. Cardiac monitoring should be considered, and rasburicase should be considered if uric acid levels remain elevated
- Clinical TLS is defined as the presence of laboratory TLS plus ≥ 1 of these criteria in the absence of other causes.
  - Serum creatinine ≥ 1.5 times the upper limit of the age-adjusted normal range
  - Symptomatic hypocalcemia
  - Cardiac arrhythmia
  - If Clinical TLS exists, manage with IV fluids, laboratory blood tests every 6 to 8 hours, cardiac monitoring, rasburicase/allopurinol/febuxostat and inpatient care (consider ICU)

Criteria modified from Cairo and Bishop (2004).

[redacted]

Graft-Versus-Host Disease (GVHD)

The chance of GVHD occurring is low, but it is a potential risk with CTL019 therapy. A prior study of activated donor lymphocyte infusions (*ex vivo* activated cells collected from the donor and grown in the same fashion as CTL019 but without the CAR introduction) did not show high rates of GVHD (2/18 patients with grade 3 GVHD and none with grade 4) (Porter et al 2006). Ten ALL patients have been treated to date with autologous CTL019 therapy who have had prior allogeneic hematopoietic SCT with residual donor chimerism. None of these patients developed GVHD after CTL019 infusion.

As part of the exclusion criteria for this protocol regarding GVHD, the grading & staging assessment of acute GVHD will follow the criteria described below in Table 6-3, and the definition of chronic GVHD will follow the criteria described in Table 6-4.

Table 6-3 Staging and grading of acute Graft-Versus-Host Disease

Extent of organ involvement			
	Skin	**Liver**	**Gut**
Stage			
1	Rash on < 25% of skin[a]	Total bilirubin 2-3 mg/dL[b]	Diarrhea > 500 mL/day[c] or persistent nausea[d]
2	Rash on 25-50% of skin	Total bilirubin 3-6 mg/dL	Diarrhea > 1,000 mL/day
3	Rash > 50% of skin	Total bilirubin 6-15 mg/dL	Diarrhea > 1,500 mL/day
4	Generalized erythroderma with bullous formation	Total bilirubin > 15 mg/dL	Severe abdominal pain with or without ileus
Grade[e]			
I	Stage 1-2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III		Stage 2-3 or	Stage 2-4
IV[f]	Stage 4 or	Stage 4	

a. Use “rule of nines” or burn chart to determine extent of rash.
b. Range given as total bilirubin. Downgrade by 1 stage if an additional cause of elevated bilirubin has been documented.
c. Volume of diarrhea applies to adults. For pediatric patients, the volume of diarrhea should be based on body surface area. Gut staging for pediatric patients was not discussed at the Consensus Conference. Downgrade by 1 stage if an additional cause of diarrhea has been documented.
d. Persistent nausea with histologic evidence of GVHD in the stomach or duodenum.
e. Criteria for grading given as a minimum degree of organ involvement required to confer that grade.
f. Grade IV may also include lesser organ involvement but with extreme decrease in performance status.

[redacted]

Table 6-4 Definitions of chronic Graft-Versus-Host Disease

Chronic GVHD is an immune-mediated disorder that may occur following allogeneic SCT. Manifestations include scleroderma, dry eyes, dry mouth, lichenoid oral changes, bronchiolitis obliterans, vanishing bile ducts, or weight loss. It is to be diagnosed specifically rather than diagnosed when acute GVHD-like syndromes develop late (beyond day +100) after any transplant or donor leukocyte infusion.

Definite and Possible Manifestations of Chronic GVHD		
Organ System	**Definite Manifestations of Chronic GVHD**	**Possible Manifestations of Chronic GVHD**
Skin	Scleroderma (superficial or fasciitis), lichen planus, vitiligo, scarring alopecia, hyperkeratosis pilaris, contractures from skin immobility, nail bed dysplasia	Eczematoid rash, dry skin, maculopapular rash, hyperpigmentation, hair loss
Mucous membranes	Lichen planus, non-infectious ulcers, corneal erosions/non-infectious conjunctivitis	Xerostomia, keratoconjunctivitis sicca
Gastrointestinal (GI) tract	Esophageal strictures, steatorrhea	Anorexia, malabsorption, weight loss, diarrhea, abdominal pain
Liver	None	Elevation of alkaline phosphatase, transaminitis, cholangitis, hyperbilirubinemia
Genitourinary (GU)	Vaginal stricture, lichen planus	Non-infectious vaginitis, vaginal atrophy
Musculo-skeletal/ Serosa	Non-specific arthritis, myositis, myasthenia, polyserositis, contractures from joint immobilization	Arthralgia
Hematologic	None	Thrombocytopenia, eosinophilia, autoimmune cytopenias
Lung	Bronchiolitis obliterans	Bronchiolitis obliterans with organizing pneumonia, interstitial pneumonitis
1. At any time point post-transplant, if there are ANY definite symptoms (column 2) then the symptoms should be identified as chronic GVHD. 2. At any time point post-transplant, if there are any possible symptoms (column 3) but no definite symptoms, then it is at the physicians' discretion to identify as either acute or chronic GVHD. 3. Acute and chronic GVHD cannot be present at the same time. Thus if #1 is fulfilled, then all manifestations of GVHD should be identified as chronic GVHD.		

Limited Chronic GVHD

- Localized skin involvement and/or liver dysfunction **OR**
- Involvement of only one target organ

Extensive Chronic GVHD

- Generalized skin involvement ≥ 50% of body surface area **OR**
- Localized skin involvement and/or liver dysfunction **plus at least one** of the following:
  - Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis
  - Eye involvement (Schirmer's test with < 5 mm wetting)
  - Involvement of minor salivary glands or oral mucosa on lip biopsy
  - Involvement of any other target organs **OR**

[redacted]

- Involvement of at least two target organs

B cell depletion

Depletion of B cells with resulting hypogammaglobulinemia is expected as a result of CTL019 on target effects in patient with sustained tumor response. CTL019 related hypogammaglobulinemia is typically managed with immunoglobulin replacement therapy dependent upon age specific, disease specific and local institutional guidelines. Immunoglobulin replacement during the study period will be recorded. In general B cell aplasia and hypogammaglobulinemia, of various causes, can be associated with increased rates of infection. Such infections are typically sinopulmonary but other sites and types of infections have also been reported.

Other potential complications of B cell aplasia include progressive multifocal leukoencephalopathy (PML) and reactivation of hepatitis B virus. Neither PML nor reactivation of hepatitis B virus have been seen yet with CTL019, however, other therapies associated with B cell aplasia have seen these complications.

For the first 12 months following CTL019 infusion, data on all significant infections will be collected for patients in the primary follow-up. After 12 months following CTL019 infusion or if patients move to the secondary follow-up prior to month 12, data on infections will only be collected when they are opportunistic or serious and requiring intervention as defined:

1. Requires anti-infective treatment
2. Leads to significant disability or hospitalization
3. Needs surgical or other intervention

6.2.4.3 Potential toxicities

Replication-competent lentivirus (RCL) testing

An RCL may be generated during CTL019 manufacturing or subsequently after introduction of vector transduced cells into the patient. However, an RCL resulting from manufacturing is highly unlikely since elements are incorporated in the design of the vector system that minimize vector recombination and generation of RCL. Furthermore, the vector used to transduce the product undergoes sensitive assays for detection of RCL before it can be released to a patient. Thus patients will only receive cell products that meet RCL release criteria. Nevertheless, generation of an RCL following infusion of the vector product remains a theoretical possibility. The development of RCL could pose a risk to both the patient and their close contact(s), and therefore, monitoring for RCL will be conducted during the course of the trial (see [Laboratory Manual] for a description of the assays). If a positive RCL assay result is obtained from a patient blood specimen, (as detected by Vesicular Stomatitis Virus/Glycoprotein (VSV-G) q-PCR, for example) the Investigator will be informed and the patient rescheduled for a retest of the DNA test. Regulatory agencies and the gene therapy community have previously discussed measures to be taken should an RCL be confirmed in a patient. However, because the probability and characteristics of an RCL are unknown, no guidelines have been put in place. Nevertheless, all agree that the patient must be isolated until an understanding of how to manage the patient becomes clear. Some considerations are:

[redacted]

- Intensive follow-up of the patient in consultation with gene therapy experts, study investigators, and Health Authorities
- Inform local and country specific public health officials
- Identify sexual partners and provide appropriate counseling and intervention

Clonality and insertional oncogenesis

The occurrence of adverse events caused by insertional mutagenesis in three patients in a gene therapy trial for X-linked Severe Combined Immunodeficiency (SCID) following stem cell therapy emphasizes the potential for problems in translating this approach to the clinic. To date, clinically evident insertional mutagenesis has not been reported following adoptive infusion of engineered T cells. Lentiviral vectors may have a lower risk than oncoretroviral vectors based on several considerations. Monitoring for T cell clonal outgrowth will be performed by q-PCR quantitation of the CTL019 transgene, and by complete blood count (CBC). If monoclonality is found, further studies including insertion site analysis will be considered.

Uncontrolled T cell proliferation

CTL019 transduced cells could theoretically proliferate without the control of normal homeostatic mechanisms. In pre-clinical studies (Milone et al 2009) and clinical experience to date (Porter 2011, Grupp 2013), CTL019 transduced cells have only proliferated in response to physiologic signals or upon exposure to CD19 antigen. In the context of CTL019 therapy, it is expected that the T cells will proliferate in response to signals from the CD19 expressing malignant tumor and normal B cells. This could be beneficial or harmful depending on the extent of proliferation. Clonal dominance of adoptively transferred T cells has been associated with tumor reduction in adoptive transfer trials (Dudley 2002, Dudley 2005).

If uncontrolled T cell proliferation occurs (e.g. expansion of T cells in the absence of CD19 antigen), patients may be treated with corticosteroids such as methylprednisolone (2 mg/kg/d i.v.) or chemotherapy, such as high dose cyclophosphamide. Investigators should further discuss this with the sponsor. Toxicity associated with allogeneic or autologous T cell infusions has been managed with a course of pharmacologic immunosuppression. T cell associated toxicity has been reported to respond to systemic corticosteroids (Lamers et al 2006). This theoretical toxicity is distinct from the toxicity associated with a CRS that develops during T cell proliferation upon exposure to CD19 expressing cells. CRS associated with T cell expansion is managed with anti-cytokine therapy, not immunosuppressants, and is addressed in Section 6.2.4.2.

Patients with CD19 CAR transgene levels equal [redacted]

[redacted] Identified vector integration sites will be evaluated using bioinformatic approaches to determine the frequency of integration events in regions with known [redacted]

relationships to human cancers (i.e. near oncogenes). If integration site analysis reveals mono- or oligo-clonality pattern and/or integration at or near an oncogenic locus, a monitoring plan, including follow-up molecular analyses, will be developed in collaboration between the Investigator, Sponsor and Health Authorities that is specific for the health care risks that are anticipated given the nature of the integration site and vector target cell type.

Immunogenicity

Immunogenicity of the CAR polypeptide has been described in several studies (Park 2007, Lamers 2006, Lamers 2007, Lamers 2011) Host immune responses may result from presentation of CAR transgene expressed immunogenic epitopes including murine sequences in the scFV extracellular binding domain (derived from a murine monoclonal antibody) or novel epitopes arising at junctions between components of the CAR fusion polypeptide. Transgene and vector specific B and T cell immune responses have been previously observed in CAR modified autologous T cell therapies even when lymphodepleting regimens were used prior to infusion. If an immune response to the CTL019 cells occurs, it is possible that the cells might be rejected. Such immune responses could also have effects such as attenuating the responsiveness of CTL019 cells by causing an immune mediated deletion of the CTL019 cells. Six of 7 evaluable patients had evidence of human anti-CAR antibody directed to the murine monoclonal antibody derived scVF in CAIX specific CAR T therapy for renal cell carcinoma (Lamers et al 2011). A single patient experienced an anaphylactic reaction after multiple, repeated injections of a CAR with a murine based scFv (Maus et al 2013). Impaired function of CEA- targeting autologous T cells has been observed *in vitro* following exposure to receptor specific IgG obtained from treated patients. (Parkhurst et al 2011)

Immunogenicity (humoral and cellular) will be measured following CTL019 infusions as indicated in the Visit Evaluation Schedule.

Immunoglobulin depletion

Transient or permanent B cell depletion is a risk with CTL019 therapy, since normal B cells express CD19. This is expected to resolve if and when the CTL019 cells are cleared. Patients may require periodic infusions of immunoglobulin based upon local and age specific guidelines for specific patient populations.

Progressive multifocal leukoencephalopathy (PML)

PML is rare but well described with antibodies causing B cell aplasia (Weissert 2011) and is a demyelinating disease of the central nervous system, resulting from infection of oligodendrocytes and astrocytes, mostly with JC virus. PML classically has a subacute clinical presentation with focal neurologic deficits, such as weakness, speech difficulties, unsteady gait and hemiparesis. Ophthalmic symptoms are relatively common, occurring as homonymous hemianopia which progresses to cortical blindness. Seizure and headache are uncommon. Dementia manifesting as mental deficits in cognition, personality changes, and memory impairment are also common, but it is almost invariably associated with the focal neurologic deficits of PML. By CT or MRI radiographic assessment, lesions are confined to the white matter, most commonly of the occipitoparietal lobe and without mass effect.

[redacted]

In general, patients with known B cell aplasia are at increased risk for PML. Therefore patients in the study will be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. Consultation with a neurologist should be considered as clinically indicated.

Hepatitis B reactivation

Reactivation of hepatitis B refers to the abrupt increase in hepatitis B virus (HBV) replication in a patient with inactive or resolved hepatitis B. Reactivation can occur spontaneously, but more typically is triggered by immunosuppressive therapy of cancer, autoimmune disease, or organ transplantation. Reactivation can be transient and clinically silent, but often causes a flare of disease that can be severe resulting in acute hepatic failure. Most instances of reactivation resolve spontaneously, but if immune suppression is continued, re-establishment of chronic hepatitis occurs which can lead to progressive liver injury and cirrhosis. Reactivation is defined as increase of one log in HBV-DNA relative to baseline HBV-DNA or new appearance of measurable HBV-DNA (Hoofnagle 2009). Patients with evidence of reactivated hepatitis B should initiate either tenofovir or entecavir, and pursue appropriate consultation.

In general, the risk of hepatitis B reactivation is increased in patients with B cell depletion. Patients with latent or active hepatitis B are typically excluded from CTL019 treatment protocols; however infection could potentially occur following the treatment trial completion or early withdrawal. Therefore, patients with a history of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection. Standard guidelines should be followed for the treatment of active/reactivated hepatitis B (Hoofnagle 2009).

Individuals with evidence of prior unresolved or ongoing HBV infection (See Section 14.2, Table 14-4) are at increased risk of reactivation of HBV infection (Patel 2015) and are excluded from this study.

New or secondary malignancies

There is a theoretical concern that transduction of a patient's T-cells with CD19 CAR lentiviral vector could result in an oncogenic effect within these T-cells that could result in a T-cell leukemia or lymphoma. Best attempts will be made to obtain fresh tumor tissue to analyze for the presence of CD19 CAR transgene in a new T-cell malignancy.

6.2.5 Criteria for discontinuing a patient's participation in the study

If a patient develops a condition that precludes CTL019 infusion after enrollment but before infusion, the patient will be prematurely discontinued. This will be done at the judgment of the PI, and could include for example, the occurrence of an intercurrent illness requiring the institution of systemic immunosuppression.

[redacted]

6.2.6 Concomitant therapy

Clinically significant prescription and nonprescription medications, excluding vitamins, herbal and nutritional supplements, and procedure-related (inpatient or outpatient) medications taken by the patient during the 30 days prior to screening will be recorded. At every visit following the screening visit up to the month 60 visit, concomitant medications will be recorded in the medical record and on the appropriate CRF. During selected trial phases, concomitant medication collection will be modified as outlined in Appendix 3: CTL019 Modified Data Reporting- Treatment and Primary Follow Up Phase, CRF Completion Guidelines (CCGs), and Table 6-5 below. Modified collection of concomitant medications during these trial phases are designed to capture CTL019-related toxicity, severity, interventions and response/resolution following intervention. Any additions, deletions, or changes of these medications will be documented.

Table 6-5 Concomitant medication reporting by trial phase

Trial phase	Inpatient/ICU	Outpatient
Pre-treatment period (ICF to LD chemo/pre-infusion)	Modified	Modified
Treatment period (LD chemo/pre-infusion through M12)	Modified	All concomitant medications
Post-treatment period (after M12 through M60)	Modified	Modified

The following guidelines must be adhered to during the study:

- Granulocyte macrophage-colony stimulating factor (GM-CSF) should be avoided due to the potential to worsen CRS symptoms.
- Short acting granulocyte colony stimulating factor (G-CSF) should not be given within 72 hours of CTL019 infusion and until CRS is resolved. Long acting G-CSF should not be given within 10 days of CTL019 infusion and until CRS is resolved. The effects of granulocyte colony stimulating factor (G-CSF) are unknown.
- Steroids or other immunosuppressant drugs should NOT be used as pre-medication for CTL019 therapy (refer to Section 6.1.1.2) or following CTL019 infusion, except as required for physiological glucocorticoid replacement therapy, or under life threatening circumstances. Use of steroids with blood product administration should be eliminated just prior to and following CTL019 if possible or at least minimized.
- Patients with moderate to severe signs and symptoms attributable to CRS should be managed with supportive care and administration of tocilizumab as defined in Figure 6-1 and Section 6.2.4.2.

6.2.7 Prohibited concomitant therapy

Concurrent use of systemic steroids or immunosuppressant medications are prohibited under this protocol except as required for physiologic replacement of hydrocortisone, or in the case of a life threatening emergency, since this may have an adverse effect of CTL019 cell expansion and function.

Specifically, the following medications are excluded:

a. **Steroids:** Therapeutic systemic doses of steroids must be stopped > 72 hours prior to CTL019 infusion. However, the following physiological replacement doses of steroids are allowed: < 12 mg/m^2/day hydrocortisone or equivalent

[redacted]

b. **Allogeneic cellular therapy:** Any donor lymphocyte infusions (DLI) must be completed > 6 weeks prior to CTL019 infusion
c. **GVHD therapies:** Any systemic drug used for GVHD must be stopped > 4 weeks prior to CTL019 infusion to confirm that GVHD recurrence is not observed (e.g. calcineurin inhibitors, methotrexate or other chemotherapy drugs, mycophenolyate, rapamycin, thalidomide, or immunosuppressive antibodies such as anti-CD20 (rituximab), anti-TNF, anti-IL6 or anti-IL6R, systemic steroids)
d. **Chemotherapy:**
   - Tyrosine kinase inhibitors and hydroxyurea must be stopped > 72 hours prior to CTL019 infusion
   - The following drugs must be stopped > 1 week prior to CTL019 infusion and should not be administered concomitantly or following lymphodepleting chemotherapy: vincristine, 6-mercaptopurine, 6-thioguanine, methotrexate < 25 mg/m^2, cytosine arabinoside < 100 mg/m^2/day, asparaginase (non-pegylated)
   - The following drugs must be stopped > 2 weeks prior to CTL019 infusion: salvage chemotherapy (e.g. clofarabine, cytosine arabinoside > 100 mg/m^2, anthracyclines, cyclophosphamide, methotrexate ≥ 25 mg/m^2), excluding the required lymphodepleting chemotherapy drugs
   - Pegylated-asparaginase must be stopped > 4 weeks prior to CTL019 infusion
e. **CNS disease prophylaxis:**
   - CNS prophylaxis treatment must be stopped > 1 week prior to CTL019 infusion (e.g. intrathecal methotrexate)
f. **Radiotherapy:**
   - Non-CNS site of radiation must be completed > 2 weeks prior to CTL019 infusion
   - CNS directed radiation must be completed > 8 weeks prior to CTL019 infusion
g. **Anti T-cell Antibodies:** Administration of any T cell lytic or toxic antibody (e.g. alemtuzumab) within 8 weeks prior to CTL019 is prohibited since residual lytic levels may destroy the infused CTL019 cells and/or prevent their in vivo expansion. If such an agent has been administered within 8 weeks prior to CTL019, contact the Sponsor, consider consultation with an pharmacology expert, and consider measuring residual drug levels, if feasible, prior to CTL019 infusion.

6.3 Dose modifications

6.3.1 Dose modifications and dose delays

Not applicable.

6.3.2 Follow-up for toxicities

6.3.2.1 Liver safety monitoring

Following CTL019 infusion, transient and reversible changes in ALT, AST, and total bilirubin (TBIL) are typically observed in parallel with the course of cytokine release syndrome (CRS). These LFT abnormalities should be followed until return to baseline values.

[redacted]

CTL019 therapy is a single, one-time infusion and CRS resolution has typically occurred by 8 weeks. If these LFT abnormalities are observed within the first 8 weeks following CTL019 infusion and are explicable by CRS, further diagnostic work up is typically not warranted.

For patients following CTL019 infusion whose LFT abnormalities are not explained by CRS or new LFT abnormalities are observed after 8 weeks post CTL019 infusion and up to 1 year, the below general guidelines should be considered. Patients with significant transaminase increase combined with significant TBIL increase may be indicative of potential hepatotoxicity, and should be considered as clinically important events. Assessments driven to finding the cause for these events is appropriate, and should be performed in a timely fashion: it may be appropriate to have a consultation with a hepatologist. Initial efforts may include:

- Repeating the LFT to confirm elevation (or decrement) as appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

The threshold for potential toxicity may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT or AST or TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN, or ALT or AST >5.0 x ULN in isolation.
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as alkaline phosphatase (ALP) elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic or hepatocellular liver injury).

In the absence of cholestasis, these patients should have repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, a renewed detailed history, renewed physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc should be considered.

- Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
- A detailed history, including relevant information, such as review of alcohol consumption, illicit drug use, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

[redacted]

- Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) such as a right upper quadrant (RUQ) ultrasound with duplex for flow, may be warranted.
- If bilirubin elevation is an isolated event (no transaminase elevations above baseline is seen), then a work-up for hemolysis is appropriate (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin).
- Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

Upon informed consent/assent completion, the patient will initiate screening. Each patient is identified in the study by a seven digit Subject Number (Subject No.), that is assigned sequentially at each site by the site investigator or designated staff when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the four digit Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential three digit patient number suffixed to it, such that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle RDC interface.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject No. must not be reused for any other patient and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to start treatment for any reason, the reason will be documented and entered onto the appropriate CRF page.

6.4.2 Treatment assignment

This is a single-arm open-label study. Patients will be enrolled and assigned to treatment upon confirmation of all clinical eligibility, and receipt and acceptance of the apheresed product by the manufacturing facility.

6.4.3 Treatment blinding

This is an open-label study.

[redacted]

6.5 Study drug preparation and dispensation

Upon release from the manufacturing facility, the cryopreserved CTL019 cell product is shipped to the investigator. Upon receipt of the cryopreserved CTL019 cell product, inventory must be performed. The respective drug receipt form is completed and signed by personnel accepting the shipment of CTL019. It is important that the designated study staff verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable CTL019 cell product in a given shipment will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable CTL019 cell product that was supplied to the investigator's site.

The CTL019 cell product will remain in storage until the subject is available for infusion and ready (Section 6.5.2). Please note the time between product thawing and completion of the infusion should not exceed 30 minutes to maintain maximum product viability. Therefore, to ensure this timeframe, the product should be thawed in close proximity to the patient's bedside. Additionally, after cell thawing the CTL019 cell product should **NOT** be washed prior to infusion. All contents must be infused. If the CTL019 cell product appears to have a damaged or leaking bag, or otherwise appears to be compromised, it should not be infused, and should be disposed of according to local institutional standard operating procedures.

For further details on product receipt, storage, preparation, and administration, see Section 6.1.1.2 and the [Investigational Product Handling Manual] (e.g. option of syringe-based administration for pediatric patients with small product volumes).

6.5.1 Study drug packaging and labeling

Each infusion bag will typically contain 10 – 50 mL of cells containing a cell dose of 0.2 to 5.0 x 10^6 autologous CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 0.1 to 2.5 x 10^8 CTL019 transduced viable T cells (for patients > 50 kg). Higher volumes may occasionally be necessary depending on transduction efficiency.

Each infusion bag will have affixed to it a label containing the following: A product identifier, the proper name of the product, and appropriate product modifiers and attributes according to the International Standard for Blood and Transplant (ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Description, Version 4.28). The study number and the wording "FOR AUTOLOGOUS USE ONLY" will be included in the label. In addition the label will have at least two unique identifiers such as the patient's alphanumeric identifier and birth date according to applicable regulations. Additional label elements required by local regulatory guidelines will also be included. Prior to the infusion, two individuals will verify all of this information and confirm identity according to local institutional guidelines, to ensure that the information is correctly matched to the patient, and that the patient receives only their autologous product.

6.5.2 Drug supply and storage

CTL019 cell product must be received, handled and stored safely and properly by designated personnel at the study site, CTL019 must be kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the CTL019 cell product

[redacted]

should be stored according to the instructions specified on the product labels and in the [Investigational Product Handling Manual].

6.5.3 Study drug compliance and accountability

Novartis has established methods to ensure full traceability between the patient's autologous apheresis and the CTL019 product in line with the requirements outlined in 21 CFR1271.250, 21CFR1271.290, Regulation (EC) 1394/2007, the Directive 2004/23/EC as well as the rules and principles of the EU "Detailed guidelines on good clinical practice specific to advanced therapy medicinal products." The data contributing to the full traceability of the cells are stored for a minimum of 30 years. Any product quality complaints are documented by the clinical site and reported to the Novartis Clinical Supplies Quality Assurance (QA) Department. A unique patient identifier will be used in order to maintain the chain of identity between the autologous apheresis product and the CTL019 batch, and the link between patient identity and unique patient identifier will be confirmed prior to infusion. The [Investigational Product Handling Manual], [Leukapheresis, Cryopreservation & Scheduling Manual], and [Investigational Product Transport Manual] provides an overview of how the company ensures that the cells which are procured, processed, stored, and distributed by or on behalf of the Novartis can be traced from donor to recipient and vice versa.

6.5.3.1 Study drug compliance

As a single administration study, compliance will be assessed by the investigator and/or study personnel and captured on site infusion records and drug accountability records.

6.5.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of CTL019 cell product in a drug accountability log. Drug accountability records will be reviewed by the field monitor during site visits and at the completion of the study.

The investigator will dispose of used and unused CTL019 cell product, packaging, product labels per local institutional standard operating procedures, and return a copy of the completed drug accountability log to the study monitor. Please refer to [Investigational Product Handling Manual] for specific details on product destruction.

6.5.3.3 Handling of other study treatment

Not applicable.

6.5.4 Disposal and destruction

CTL019 cell product may require disposal for a variety of reasons, including but not limited to: 1) Mislabeled product; 2) Condition of patient prohibits infusion, and/or 3) Patient refuses infusion. Any unused product and all used infusion supplies, including the infusion bag and tubing, must be disposed of according to local institutional standard operating procedures. For further details, please refer to the specific guidance provided in the [Investigational Product Handling Manual].

[redacted]

Reconciliation of CTL019 cell product shipped, consumed, and remaining, is performed by Novartis. This information is submitted on an annual basis to the health authorities in annual reports. All CTL019 cell product disposition will be documented in the study files. Please refer to [Investigational Product Handling Manual] for details on product reconciliation.

7 Visit schedule and assessments

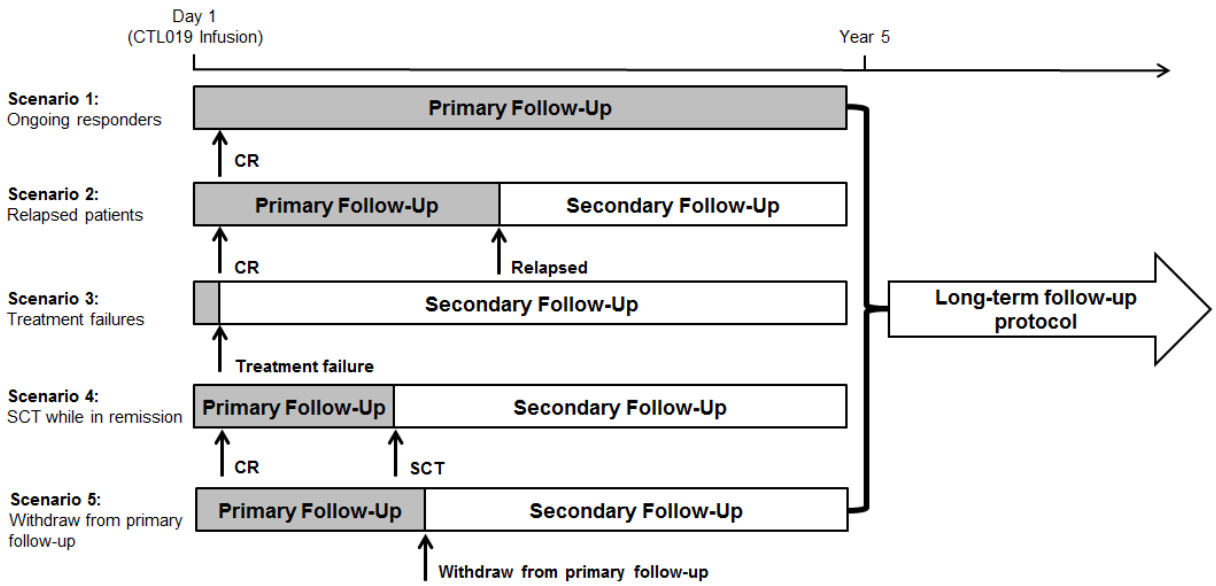
7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments through the end of the Treatment and Primary Follow-up phase (Section 7.1.3).

For patients who discontinue early from the Treatment and Primary Follow-Up Phase prior to Month 60, the patient will enter a Secondary Follow-Up Phase to collect health authority requested data (e.g. delayed adverse events, etc.). The first visit in the Secondary Follow-Up Phase is determined according to the time since CTL019 infusion when the patient discontinued from the Treatment and Primary Follow-Up Phase. For example, if the patient discontinued from the Treatment and Primary Follow-Up phase at Month 10, the first visit in the Secondary Follow-Up Phase will be Month 12. Table 7-2 lists all of the assessments through the end of the Secondary Follow-up phase (Section 7.1.4). It is anticipated that patients may leave the primary follow-up and move to secondary follow-up due to reasons including: treatment failure, relapse after remission, pursuing SCT while in remission, or withdrawal from the primary follow-up (See Figure 7-1 below).

In each table, required assessments are indicated with an "X", and the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. No CRF will be used as a source document.

Figure 7-1 Potential patient flow scenarios



[redacted]

Table 7-1 Visit evaluation schedule: treatment and primary follow-up

Phase	**Category**	**Protocol Reference Section**	**Screening**	**Pre-Treatment**			**Treatment and Primary Follow-up**															**Survival Follow-up**
Visit Name			**Screening**	**Enrollment/Pre-chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**													**End of Treatment & Primary Follow-up**	**Survival Follow-up After study completion**
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
Obtain Informed Consent/Assent	D	11.3.	X																			
IWRS/IRT	S	7.1.1.1.	X	X			X		X	X	X	X		X	X	X M3 & M6 only	X					
Patient history																						
Demography	D	7.1.1.	X																			
Inclusion/exclusion criteria	D	5.2. 5.3.	X																			
Medical history	D	7.1.1.	X																			
Diagnosis and extent of cancer	D	7.1.1.	X																			
Cytogenetics/FISH/Tumor Immunophenotyping	D	7.1.1.	X																			
Prior antineoplastic therapy	D	7.1.1.	X																			

[redacted]

Phase	**Category**	**Protocol Reference Section**	**Screening**	**Pre-Treatment**			**Treatment and Primary Follow-up**														**Survival Follow-up**
Visit Name			**Screening**	**Enrollment/Pre-chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**												**End of Treatment & Primary Follow-up**	**Survival Follow-up After study completion**
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
Donor chimerism (prior allogeneic SCT patients only, or if unknown)	D	6.2.4.2. 7.1.1.	X																		
Prior/concomitant medications	D	6.2.6.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination (PE)	S	7.2.1.1.	X			X		X		X		X		X	X	X	X	X	X	X	X	
Performance status assessment	D	7.2.2.3.	X			X		X		X		X		X	X	X	X	X	X	X	X	
Height	D	7.2.2.2.	X													X M6 only	X M12 only	X M18 only	X	X	X	
Tanner staging (only for patients < 18 years old)	D	7.2.2.	X													X M6 only	X M12 only	X M18 only	X	X	X	
Weight	D	7.2.2.2.	X			X									X	X M3 & M6 only	X	X M18 only	X	X	X	
Vital signs	D	7.2.2.1.	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[redacted]

Phase	**Category**	**Protocol Reference Section**	**Screening**	**Pre-Treatment**			**Treatment and Primary Follow-up**														**Survival Follow-up**
Visit Name			**Screening**	**Enrollment/Pre-chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**												**End of Treatment & Primary Follow-up**	**Survival Follow-up After study completion**
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
PedsQL and EQ-5D Questionnaire	D	7.2.7.		X											X	X M3 & M6 only	X	X M18 only	X		X	
Hospitalization status	D	7.2.6.	Hospitalizations from Screening to Month 2																			
Intervention																						
Lymphodepleting Chemotherapy	D	6.1.1.1.			X																	
Other chemotherapy while on study	D	6.2.6.	As clinically indicated																			
CTL019 infusion prerequisite assessment	S	6.1.1.2.					X															
CTL019 T cell infusion	D	6.1.1.2.					X															
Antineoplastic therapies after CTL019 infusion or study discontinuation	D	6.2.6.						X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory assessments																						
Hematology	D	7.2.2.5.	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[redacted]

Phase			**Screening**	**Pre-Treatment**			**Treatment and Primary Follow-up**														**Survival Follow-up**
Visit Name	**Category**	**Protocol Reference Section**	**Screening**	**Enrollment/Pre-chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**												**End of Treatment & Primary Follow-up**	**Survival Follow-up After study completion**
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
Chemistry	D	7.2.2.5.	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Lab tests of special interest during CRS only (CRP, ferritin, fibrinogen, LDH, PT, aPTT, INR, D-dimer)	D	7.2.2.5.					X	X	X	X	X	X	X	X	X							
Serum pregnancy test	D	7.2.2.5.	X																			
Serum or Urine pregnancy test	D	7.2.2.5.				X																
HIV Test	D	7.2.2.5.	X																			
Hepatitis B and C	D	7.2.2.5.	X																			
Influenza A and B	D	6.1.1.2. 7.1.2.		Within 10 days of infusion																		
Coagulation factors (PT, aPTT, INR, fibrinogen, D-dimer)	D	7.2.2.5.	X		X		X			X		X			X							
Serum immunoglobulin levels (IgG, IgA, IgM)	D	7.2.2.5.	X									X			X	X M3 & M6 only	X					

[redacted]

Phase			**Screening**	**Pre-Treatment**			**Treatment and Primary Follow-up**														**Survival Follow-up**
Visit Name	**Category**	**Protocol Reference Section**	**Screening**	**Enrollment/Pre-chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**												**End of Treatment & Primary Follow-up**	**Survival Follow-up After study completion**
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
MUGA/ECHO	D	7.1.1.	X																		
Electrocardiogram (ECG)	D	7.1.1.	X				X														
Urinalysis	D	7.2.2.5.	X																		
Pulse oximetry	D	7.2.2.1.	X				X														
Disease Assessments																					
Bone Marrow biopsy and aspirate morphology	D	7.2.1.	X												X	If patient is not in CR/CRi at D28, then **required** at the first time clinical evidence of remission is seen by blood and PE. For patients in CR/CRi, Month 3 and 6 recommended but not required						
MRD assessment in bone marrow aspirate by flow cytometry (includes normal B cell counts and CD19 status)	D	7.2.1.	X												X	If patient is not in CR/CRi at D28, then **required** at the first time clinical evidence of remission is seen by blood and PE. For patients in CR/CRi, Month 3 and 6 recommended but not required						

[redacted]

Phase	**Category**	**Protocol Reference Section**	**Screening**	**Pre-Treatment**			**Treatment and Primary Follow-up**														**Survival Follow-up**
Visit Name			**Screening**	**Enrollment/Pre-chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**												**End of Treatment & Primary Follow-up**	**Survival Follow-up After study completion**
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
MRD assessment in bone marrow aspirate by qPCR	D	7.2.1.	X												X	If patient is not in CR/CRi at D28, then **required** at the first time clinical evidence of remission is seen by blood and PE. For patients in CR/CRi, Month 3 and 6 recommended but not required						
Tumor cell assessment by flow cytometry of peripheral blood (includes normal B cell counts and CD19 status)	D	7.2.1.	X							X		X		X	X	X M3 & M6 only	X	X M18 only	X	X	X	
Lymph node or other involved tissue aspirate or biopsy	D	7.2.1.	As clinically indicated																		
CSF assessment by lumbar puncture	D	7.2.1.	X												X	If patient is not in CR/CRi at D28, then **required** at the first time clinical evidence of remission is seen by blood and PE. Otherwise, as clinically indicated by the presence of neurologic symptoms.						
CNS Brain Imaging (MRI/CT)	S	7.2.1.	As clinically indicated																		

[redacted]

Phase			**Screening**	**Pre-Treatment**			**Treatment and Primary Follow-up**														**Survival Follow-up**
Visit Name	**Category**	**Protocol Reference Section**	**Screening**	**Enrollment/Pre-chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**												**End of Treatment & Primary Follow-up**	**Survival Follow-up After study completion**
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
Extramedullary disease assessment (physical exam and CNS symptom assessment)	D	7.2.1.1. 7.2.1.2.	X												X	X	X	X	X	X	X	
Safety																						
Adverse events	D	8.1.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancies and menstrual status	D	7.2.2.		X												X	X	X	X	X	X	
Immunogenicity (serum)	D	7.2.2.5. 10.5.3.4.		X								X			X	X M3 & M6 only	X M12 only	If patient relapses at any time point (before or after Month 12), then immunogenicity sample collection required at relapse visit.				
Immunogenicity (peripheral blood)	D	7.2.2.4. 10.5.3.4.		X								X			X	X M3 & M6 only	X M12 only	Xf patient relapses at any time point (before or after Month 12), then immunogenicity sample collection required at relapse visit.				

[redacted]

Phase	**Category**	**Protocol Reference Section**	**Screening**	**Pre-Treatment**			**Treatment and Primary Follow-up**														**Survival Follow-up**
Visit Name			**Screening**	**Enrollment/Pre-chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**												**End of Treatment & Primary Follow-up**	**Survival Follow-up After study completion**
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
RCL by VSV-G q-PCR (peripheral blood)	D	6.2.4.3.		X												X M3 & M6 only	X M12 only		X		X	
Biomarkers																						
Cytokines (serum)	D	7.2.4.		X			X	X	X	X		X		X	X	X M3 & M6 only	X M12 only					
CRS assessments by peripheral blood (anti-cytokine therapy PK, CTL019 PK, cytokines, IL-6R and inflammatory markers)	D	7.1.3.					As clinically indicated dependent upon the presence and time-course of CRS and administration of anti-cytokine therapies – refer to Table 7-7, Table 7-8, Table 7-15, Table 7-16, Table 7-17.															
CTL019 pharmacokinetics by q-PCR (peripheral blood)	D	7.2.3.		X			X		X	X	X	X		X	X	X M3 & M6 only	X	X M18 only	X	X	X	

[redacted]

Phase			**Screening**	**Pre-Treatment**			**Treatment and Primary Follow-up**														**Survival Follow-up**
Visit Name	**Category**	**Protocol Reference Section**	**Screening**	**Enrollment/Pre-chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**												**End of Treatment & Primary Follow-up**	**Survival Follow-up After study completion**
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
CTL019 pharmacokinetics and normal T cells by flow cytometry (peripheral blood)	D	7.2.3.		X					X	X	X	X		X	X	X M3 & M6 only	X	X M18 only	X	X	X	
CTL019 pharmacokinetics by q-PCR (bone marrow aspirate)	D	7.2.3.	X												X	If patient is not in CR/CRi at D28, then **recommended** at the first time clinical evidence of remission is seen by blood and PE. For patients in CR/CRi, Month 3 and 6 recommended but not required						
CTL019 pharmacokinetics by flow cytometry (bone marrow aspirate)	D	7.2.3.	X												X	If patient is not in CR/CRi at D28, then **recommended** at the first time clinical evidence of remission is seen by blood and PE. For patients in CR/CRi, Month 3 and 6 recommended but not required						
CTL019 pharmacokinetics by q-PCR (CSF)	D	7.2.3.	X												X	If patient is not in CR/CRi at D28, then **recommended** at the first time clinical evidence of remission is seen by blood and PE. For patients in CR/CRi, Month 3 and 6 recommended but not required						

[redacted]

Phase	**Category**	**Protocol Reference Section**	**Screening**	**Pre-Treatment**			**Treatment and Primary Follow-up**														**Survival Follow-up**
Visit Name			**Screening**	**Enrollment/Pre-chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**												**End of Treatment & Primary Follow-up**	**Survival Follow-up After study completion**
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
[redacted]	D	7.2.4.		X						X		X		X	X	X M3 & M6 only	X		X M24 & M36 only			
[redacted]	D	7.2.4.		X											X	X M3 & M6 only	X M12 only					
[redacted]	D	7.2.4.	X												X	If patient is not in CR/CRi at D28, then **recommended** at the first time clinical evidence of remission is seen by blood and PE. For patients in CR/CRi, Month 3 and 6 recommended but not required					
[redacted]	D	7.2.4.	X					For patients who relapse post infusion, this assessment will be performed on relapsed BM evaluation. If bone marrow is not available, peripheral blood can be used if tumor cells are present in the peripheral blood at relapse.													
[redacted]	D	7.2.4.	X					For patients who relapse post infusion, this assessment will be performed on relapsed BM evaluation. If bone marrow is not available, peripheral blood can be used if tumor cells are present in the peripheral blood at relapse.													

[redacted]

Phase			**Screening**	**Pre-Treatment**			**Treatment and Primary Follow-up**														**Survival Follow-up**
Visit Name	**Category**	**Protocol Reference Section**	**Screening**	**Enrollment/Pre-chemotherapy**	**Lymphodepleting Chemotherapy**	**Pre-infusion**	**Infusion**	**Post infusion**												**End of Treatment & Primary Follow-up**	**Survival Follow-up After study completion**
Study Day			**W-16 to W-12**	**W-16 to D-1**	**D-14 to D-2**	**D-1 +1d**	**D1**	**D2**	**D4 ±1d**	**D7 ±1d**	**D11 ±1d**	**D14 ±3d**	**D17 ±3d**	**D21 ±3d**	**D28 ±4d**	**M2 M3 M4 M5 M6 ±14d**	**M9 M12 ±14d**	**M15 M18 M21 ±14d**	**M24 M36 M48 ±14d**	**M30 M42 M54 ±14d**	**M60 ±14d**	**q3m ±14d**
Apheresis sample for correlative studies	D	7.2.4.		X																	
CTL019 cell product sample for correlative studies	D	7.2.4.		X																	
Survival follow-up	D	7.1.5.						For all patients who receive a CTL019 infusion, follow-up for survival every 3 months until end of study or enrolling into the long term follow-up, whichever comes first. If a patient misses a quarterly scheduled visit where survival status is required, or if the time-point does not align with a scheduled visit, survival status can be obtained via phone contact.													X
End of Phase Disposition	D	N/A	X			X														X	

[redacted]

Table 7-2 Visit evaluation schedule: secondary follow-up

For patients who end their primary follow-up before month 60:

Phase	**Category**	**Protocol Reference Section**	**Secondary Follow-up**									**Survival Follow-up**
Visit Name			**Post Infusion**								**End of Secondary Follow-up**	**Survival Follow-up after study completion**
Study Day			**M2 ±14d**	**M3 ±14d**	**M6 ±14d**	**M9 ±14d**	**M12 ±14d**	**M24 ±14d**	**M36 ±14d**	**M48 ±14d**	**M60 ±14d**	**q3m ±14d**
Patient History												
Concomitant medications (selected)	D	7.1.4.1.					X	X	X	X	X	
First antineoplastic therapy after CTL019 infusion (only for patients in remission)	D	7.1.4.	For all patients who are in remission, the first antineoplastic therapy administered (first therapy including conditioning for cell therapy (CAR, SCT) plus cell therapy (CAR, SCT) should be reported.									
Height	D	7.2.2.2.					X	X	X	X	X	
Weight	D	7.2.2.2.					X	X	X	X	X	
Tanner staging (only for patients < 18 years old)	D	7.2.2.					X	X	X	X	X	
Efficacy assessments												
Relapse information (only for patients in remission)	D	7.1.4.	For all patients who are in remission, relapse status should be assessed every 3 months until first relapse (if applicable). If a patient misses an annual scheduled visit where relapse status is required, or if the time-point does not align with a scheduled visit, relapse status can be obtained remotely.									
Safety assessments												
Protocol defined adverse events, including new malignancies and significant findings	D	7.1.4.	Protocol defined adverse events should be reported upon investigator knowledge which may not align with scheduled visits.									
Pregnancies and menstrual status	D	7.2.2.					X	X	X	X	X	
Hematology	S	7.2.2.5.					X	X	X	X	X	
Physical examination (PE)	S	7.2.1.1.					X	X	X	X	X	
CTL019 transgene persistence (peripheral blood)	D	7.2.3.		X	X	X	X	X	X	X	X	

[redacted]

Phase	**Category**	**Protocol Reference Section**	**Secondary Follow-up**									**Survival Follow-up**
Visit Name			**Post Infusion**								**End of Secondary Follow-up**	**Survival Follow-up after study completion**
Study Day			**M2 ±14d**	**M3 ±14d**	**M6 ±14d**	**M9 ±14d**	**M12 ±14d**	**M24 ±14d**	**M36 ±14d**	**M48 ±14d**	**M60 ±14d**	**q3m ±14d**
Flow Cytometry of peripheral blood (B cell, T cell levels	D	7.2.1.		X	X	X	X	X	X	X	X	
RCL by VSV-G q-PCR (peripheral blood)	D	6.2.4.3.		X	X		X	X	X	X	X	
Immunogenicity (serum)	D	7.2.2.5. 10.5.3.4.		X	X		X					
Immunogenicity (peripheral blood)	D	7.2.2.4. 10.5.3.4.		X	X		X					
Survival follow-up	D	7.1.5.	For all patients who receive a CTL019 infusion, follow-up for survival every 3 months until end of study or enrolling into the long term follow-up, whichever comes first. If a patient misses a quarterly scheduled visit where survival status is required, or if the time-point does not align with a scheduled visit, survival status can be obtained via phone contact.									X
End of phase disposition	D	N/A									X	

[redacted]

7.1.1 Screening Phase

Anti-microbial prophylaxis treatment in these immunosuppressant relapsed/refractory ALL patients should be considered per local institutional guidelines at study entry or prior to lymphodepleting chemotherapy.

Only following confirmation of all clinical eligibility criteria (defined as all inclusion/exclusion criteria except that which pertains to the leukapheresis product) will the patient's leukapheresis product be shipped to the manufacturing facility. The manufacturing facility will then evaluate the patient's leukapheresis product for acceptance.

Patients should not be enrolled if they are unwilling to be followed up long-term i.e. 15 year follow up as required by the health authorities for cell and gene therapy products.

CTL019 infusion should occur within 16 weeks of informed consent.

Patients who have signed an informed consent/assent will undergo a routine leukemia staging workup including:

a. Demography
b. Medical history (including diagnosis and extent of cancer and any prior history of CNS leukemia involvement) and prior/concomitant medications and antineoplastic therapies
c. Physical Examination (PE) including height, weight, GVHD assessment, Tanner staging (only for patients < 18 years old), vital signs, extramedullary disease assessment and CNS symptom assessment
d. Performance status (Karnofsky [age ≥16 years] or Lansky [age < 16 years]) at the time of screening
e. Standard ALL cytogenetics, FISH, and tumor immunophenotyping by flow cytometry analysis required (at the time of most recent relapse). If not available, test must be performed at screening.
f. Donor Chimerism (within 3 months of screening, prior allogeneic SCT patients only, or if unknown)
g. Complete Blood Count, Differential
h. Chemistry Panel
i. Coagulation panel
j. Urinalysis
k. Serum pregnancy test (if female of childbearing potential)
l. HIV Testing (test within 8 weeks of screening) – If an initial HIV screening test is positive then a confirmatory HIV test is required to be performed as per current local guidelines
m. Hepatitis B and Hepatitis C test (test within 8 weeks of screening; see Appendix 2 for interpretation of Hepatitis B results)
n. Serum immunoglobulin levels (IgG, IgA, IgM)
o. MUGA or ECHO (performed within 6 weeks of infusion) for LVSF/LVEF
p. ECG
q. Pulse oximetry
r. Bone marrow aspirate and biopsy for:

[redacted]

- Morphologic blast enumeration
- Flow cytometry (B-cell numbers, tumor cell numbers, MRD assessment, CD19 assessment, and CTL019 immunophenotyping)
- CTL019 PK (qPCR and flow cytometry)
- [redacted]

s. Peripheral blood collection for flow cytometry (B and T-cell numbers, tumor cell numbers, and CD19 assessment)
t. Lymph node or tissue aspirate or biopsy (if clinically indicated)
u. Lumbar Puncture (LP) for CSF cytologic assessment and CTL019 PK (by q-PCR)
v. CNS Brain Imaging (MRI/CT) (if clinically indicated)
w. Adverse events

7.1.1.1 Eligibility screening and enrollment

For detailed enrollment procedures, including use of Interactive Response Technology (IRT), please refer to the [IRT User Manual].

Once clinical eligibility has been confirmed, only then can the patient's apheresis product be shipped to the manufacturing facility. The manufacturing facility will then evaluate the patient's apheresis product for acceptance and notify the site. Enrollment is defined as the point at which a patient meets all clinical inclusion/exclusion criteria and the patient's apheresis product is received and accepted by the manufacturing facility. The patient is then enrolled using the same Subject No. assigned at screening by the site investigator or designated staff. Once assigned, the Subject No. must not be reused for any other patient and the Subject No. for that individual must not be changed. If a screened patient is not enrolled for any reason, the specific reason will be entered into the clinical database.

IRT Registration: To document screening and enrollment into the study, the IRT will be contacted initially after informed consent/assent is obtained and again after eligibility is confirmed.

7.1.1.2 Information to be collected on screening failures

The reason for not being enrolled will be entered in the clinical database. The demographic information, informed consent/assent, Inclusion/Exclusion pages, any adverse events leading to subject discontinuation, and any adverse events that meet reporting criteria in Appendix 3: CTL019 Modified Data Reporting must also be completed for patients not enrolled. No other data will be entered into the clinical database for patients who are not enrolled.

7.1.2 Pre-Treatment Phase

For details of assessments, refer to Table 7-1.

[redacted]

Enrollment/Pre-chemotherapy evaluation visit (W-16 to D-1)

Before the scheduled lymphodepleting chemotherapy regimen is to begin, the patient will undergo blood collection for safety and biomarker assessments (including CTL019 PK, immunophenotyping and tumor clonal typing, humoral & cellular immunogenicity and RCL by VSV-G qPCR). These draws can be collected at any time after informed consent is signed up until before the lymphodepleting chemotherapy is scheduled. In addition, adverse events and prior/concomitant medications will be reviewed. Viably frozen samples from the leukapheresis material as well as the CTL019 product will be collected at the manufacturing site for correlative studies. In addition, the Patient Reported Outcome questionnaires should be completed at the time of enrollment. Under extenuating circumstances where the baseline PRO questionnaire(s) was not completed at enrollment, it must be completed before the administration of LD chemotherapy or the CTL019 infusion if LD chemotherapy is not administered.

Lymphodepleting chemotherapy visit (D-14 to D-2)

It is anticipated that many patients will have been receiving chemotherapy for relapse or resistant disease. For inclusion they will have responding or stable disease to the most recent therapy. Prior to CTL019 cell infusion and after leukapheresis, an additional chemotherapy cycle is planned. Patients referred with stable disease on no recent therapy will be eligible as well. The use of additional chemotherapy prior to the recommended preinfusion chemotherapy will be at the discretion of the investigator and dependent on the patient's disease burden.

When given, lymphodepleting chemotherapy should be started before CTL019 infusion so that these cells will be given 2 to 14 days after completion of the lymphodepleting chemotherapy. The timing of chemotherapy initiation therefore depends on the length of the regimen. The purpose of the chemotherapy is to induce lymphopenia in order to facilitate engraftment and homeostatic expansion of CTL019 cells. Fludarabine (30 mg/m^2 i.v. daily for 4 doses) and cyclophosphamide (500 mg/m^2 i.v. daily for 2 doses starting with the first dose of fludarabine) is the regimen of choice, as there is the most experience with the use of this regimen in facilitating adoptive immunotherapy. Refer to Section 2.2.1 for additional information regarding lymphodepleting chemotherapy.

If patients have a WBC count ≤ 1,000 cells/µL within one week prior to CTL019 infusion, lymphodepleting chemotherapy is **NOT** required. If the time between lymphodepleting chemotherapy and CTL019 infusion exceeds **4 weeks**, lymphodepleting chemotherapy will be repeated **only** if the patients WBC count is >1,000 cells/µL.

Patients will also undergo blood tests including chemistry, a coagulation panel, and a CBC with differential. In addition, adverse events and prior/concomitant medications will be reviewed.

Pre-infusion visit (D-1 +1d)

On the day prior to or day of the scheduled CTL019 infusion, patients will undergo a physical exam (including weight and vital signs) and a performance status assessment (Karnofsky (age ≥16 years) or Lansky (age < 16 years). In addition, a urine or serum pregnancy test will be

[redacted]

performed on female patients of childbearing potential confirming a negative pregnancy result. In addition, adverse events and prior/concomitant medications will be reviewed.

Note: All patients must undergo a rapid influenza diagnostic test within 10 days prior to the planned CTL019 infusion. If the patient is positive for influenza, he/she should complete a full course of oseltamivir phosphate or zanamivir as described in the label (see Tamiflu® or Relenza® package insert for dosing). The patient must complete their full course of treatment **prior** to receiving CTL019. The test does not need to be repeated prior to CTL019 infusion however if flu-like or respiratory signs and symptoms are present, CTL019 infusion should be delayed until the patient is asymptomatic. For patients residing in the United States, Canada, Europe, and Japan, influenza testing is required during the months of October through May, inclusive. For patients residing in the Southern Hemisphere such as Australia, influenza testing is required during the months of April through November, inclusive. For patients with significant international travel, both calendar intervals may need to be considered.

7.1.3 Treatment and Primary Follow-Up Phase

For details of assessments, refer to Table 7-1.

Infusion visit (D1)

CTL019 infusions will begin 2 to 14 days after lymphodepleting chemotherapy completion and within 16 weeks after obtaining informed consent. The time elapsed from informed consent to enrollment should not exceed 4 weeks, and enrollment to infusion should not exceed 12 weeks. The total window between informed consent and CTL019 infusion must not exceed 16 weeks. If this window exceeds 16 weeks, the case must be discussed and approved by the Sponsor in order to allow for CTL019 product to be infused.

The day of (but prior to) the CTL019 infusion, patients will undergo blood tests including chemistry, a CBC with differential, a coagulation panel and serum cytokines. Final CTL019 infusion pre-requisites (including an ECG and a rapid influenza test) will be checked prior to infusion (per Section 6.1.1.2).

CTL019 transduced T cells will be given as a single dose of 0.2 to 5.0 x 10^6 CTL019 transduced viable T cells per kg body weight (for patients $\leq$ 50 kg) and 0.1 to 2.5 x 10^8 CTL019 transduced viable T cells (for patients > 50 kg). Vital signs will be monitored before and following CTL019 infusion (per Section 6.1.1.2). Blood samples will be collected post-infusion for CTL019 PK assessment. In addition, adverse events and prior/concomitant medications will be reviewed.

Details on the administration of the CTL019 infusion are found in Section 6.1.1.2.

For all patients who receive a CTL019 infusion, additional follow-up will be made to determine survival every 3 months. If a patient misses a quarterly scheduled visit where survival status is required, or if the quarterly time-point where survival status is required does not align with a scheduled visit, survival status can be obtained via phone contact.

Post-infusion visits: D2, D4±1d, D7±1d, D11±1d, D14±3d, D17±3d, D21±3d

At the intervals following infusion listed above, patients will undergo one or more of the following: blood tests including chemistry, lab tests of special interest during CRS only (CRP,

[redacted]

ferritin, fibrinogen, LDH, PT, aPTT, INR, D-dimer), hematology, coagulation, serum immunoglobulin, humoral & cellular immunogenicity, serum cytokines, CTL019 PK, immunophenotyping, flow cytometry (B and T cells, tumor cells and CD19 assessment), a physical exam (with vital signs) and performance status assessment. In addition, adverse events and prior/concomitant medications will be reviewed. On Day 2, only vital signs, physical examination, a performance status assessment, serum cytokines, hematology, and chemistry (inclusive of LFTs and creatinine) will be performed.

Sample collections for serum cytokines, CTL019 PK, and inflammatory markers (e.g. ferritin and CRP) are mandated during the first 28 days following CTL019 infusion. However, as the time-course and rapidity of CRS development varies among patients, additional unscheduled samples that might better parallel these individual differences may also be collected as needed, if it is clinically feasible. Frequent monitoring of serum CRP, ferritin, and cytokines should be considered during the clinical course of CRS of any severity (e.g. every day to several days) especially around the following clinical events: initial persistence of fevers, hemodynamic instability, initial and worsening of respiratory distress, rapid clinical deterioration, just prior to and daily for 2 days following tocilizumab administration, around other clinically significant events and upon the clinical resolution of CRS.

Please note that results of cytokine analyses are NOT to be used for clinical management decisions of CRS. A detailed treatment algorithm has been established with clear criteria for CRS management (see Figure 6-1).

For details of assessments at each visit, refer to Table 7-1.

Post-infusion visit (D28 ±4d)

Patients will undergo blood collection for hematology, chemistry, lab tests of special interest during CRS only (CRP, ferritin, fibrinogen, LDH, PT, aPTT, INR, D-dimer), coagulation, serum immunoglobulins, cytokines, flow cytometry (B and T cells, tumor cells, and CD19 assessment) humoral and cellular immunogenicity, CTL019 PK, immunophenotyping and tumor clonal typing. Patients will have a lumbar puncture for CSF cytologic assessments and CTL019 PK. Patients are required to have a bone marrow biopsy and aspirate for morphology, flow cytometry, MRD, CTL019 PK and [redacted]. In addition, patients will undergo a physical exam (including vital signs, weight, and extramedullary disease assessment), CNS symptom assessments and a performance status assessment. Tumor response assessments will be conducted (see Appendix 1 for response guidelines). A lymph node or tissue aspirate or biopsy may be done if clinically indicated. Adverse events and prior/concomitant medications will be reviewed.

For details of assessments, refer to Table 7-1.

Post-infusion visits (M2 ±14d, M3 ±14d, M4 ±14d, M5 ±14d, M6 ±14d)

At the intervals following infusion listed above, patients will undergo one or more of the following: blood collection for hematology, chemistry, serum immunoglobulins, flow cytometry (B and T cells, tumor cells, and CD19 assessment), cytokines, humoral & cellular immunogenicity and CTL019 PK, immunophenotyping, [redacted], and RCL by VSV-G qPCR. In addition, patients will undergo a physical exam (including vital signs, height, weight, Tanner staging (only for patients < 18 years old), and extramedullary disease

[redacted]

assessment), CNS symptom assessment, and a performance status assessment. Adverse events and prior/concomitant medications will be reviewed.

Following initial achievement of CR or CRi, peripheral blood and extramedullary disease assessments (physical exam and CNS symptom assessment) should be performed at a minimum of 4 weeks (28 days) after the initial achievement of CR or CRi.

If patients were not in CR or CRi at the D28 visit assessment, a bone marrow biopsy/aspirate and CSF assessment/lumbar puncture will be required for tumor response assessments at the first visit where clinical evidence of remission is observed by peripheral blood and extramedullary disease assessment (physical exam and CNS symptom assessments).

Patients may also have a bone marrow biopsy, aspirate, LP/CSF assessment and lymph node aspirate or biopsy (if accessible) at month 3 and month 6 for tumor response assessments (recommended but not required).

For details of assessments at each visit, refer to Table 7-1.

Post-infusion visit (M9 ±14d)

Patients will undergo one or more of the following: blood collection for hematology, chemistry, serum immunoglobulins, flow cytometry (B and T cells, tumor cells, and CD19 assessment), and CTL019 PK. In addition, patients will undergo a physical exam (including vital signs and extramedullary disease assessment), CNS symptom assessment and a performance status assessment. Adverse events and prior/concomitant medications will be reviewed.

For details of assessments, refer to Table 7-1.

Post-infusion visit (M12 ±14d)

Patients will undergo the following: blood collection for hematology, chemistry, serum immunoglobulins, flow cytometry (B and T cells, tumor cells, and CD19 assessment), cytokines, humoral and cellular immunogenicity, CTL019 PK, immunophenotyping, tumor clonal typing and RCL by VSV-G qPCR. In addition, patients will undergo a physical exam (including height, weight, GVHD assessment, Tanner staging (only for patients < 18 years old), vital signs, and extramedullary disease assessment), CNS symptom assessment, and a performance status assessment. Adverse events and prior/concomitant medications will be reviewed.

For details of assessments, refer to Table 7-1.

Patients with CD19 CAR transgene levels equal [redacted] Identified vector integration sites will be evaluated using bioinformatic approaches to determine the frequency of integration events in regions with known relationships to human cancers (i.e. near oncogenes). If integration site analysis reveals mono- or oligo-clonality pattern and/or integration at or near an oncogenic locus, a monitoring plan,

[redacted]

including follow-up molecular analyses, will be developed in collaboration between the Investigator, Sponsor and Health Authorities that is specific for the health care risks that are anticipated given the nature of the integration site and vector target cell type.

Post-infusion visit (M15 ±14d, M18 ±14d, M21 ±14d)

Patients will undergo the following: blood collection for hematology, chemistry and CTL019 PK. Blood will be collected for flow cytometry (B and T cells, tumor cells) at M18 only. In addition, patients will undergo a physical exam (including height, weight and Tanner staging at M18 only), vital signs, extramedullary disease assessment, CNS symptom assessment and a performance status assessment. Adverse events and prior/concomitant medications will be reviewed. Any pregnancies will be reported.

Post-infusion visit (M24 ±14d, M30 ±14d, M36 ±14d, M42 ±14d, M48 ±14d, M54 ±14d)

Patients will undergo the following: blood collection for hematology, chemistry and CTL019 PK. Blood will be collected for flow cytometry (B and T cells, tumor cells) and RCL by VSV-G qPCR annually at M24, M36 and M48 only. Blood will be collected for CTL019 immunophenotyping. In addition, patients will undergo a physical exam [including height, weight and Tanner staging (only for patients < 18 years old)], vital signs, extramedullary disease assessment, CNS symptom assessment and a performance status assessment. Adverse events and prior/concomitant medications will be reviewed. Any pregnancies will be reported.

For all patients who receive a CTL019 infusion, follow-up for survival every 3 months until end of study or enrolling into the long term follow-up, whichever comes first, is required. If a patient misses a quarterly scheduled visit where survival status is required, or if the quarterly time-point where survival status is required does not align with a scheduled visit, survival status can be obtained via phone contact.

7.1.3.1 End of Treatment and Primary Follow-Up (EOT) visit (M60 ± 14d) including premature withdrawal

The End of Treatment and Primary Follow-Up (EOT) visit for each patient will be 60 months (5 years) from the date of their infusion if they complete all scheduled visits. If a patient discontinues early from the primary follow-up, a visit should be scheduled as soon as possible, at which time all of the assessments listed for the Month 60 visit will be performed. An End of Treatment and Primary Follow-Up Disposition Case Report/ Record Form (CRF) page should be completed, giving the date and reason for stopping the study.

During the End of Treatment and Primary Follow-Up visit, patients will undergo the following: blood collection for hematology, chemistry, CTL019 PK, flow cytometry (B and T cells, tumor cells) and RCL by VSV-G qPCR. In addition, patients will undergo a physical exam [including height, weight and Tanner staging (only for patients < 18 years old)], vital signs, extramedullary disease assessment, CNS symptom assessment and a performance status assessment. Adverse events and prior/concomitant medications will be reviewed. Any pregnancies will be reported.

Following completion of the Treatment and Primary Follow-Up, patients will be followed for survival until the end of the study as defined in Section 4.2 (Section 7.1.5). Patients who

[redacted]

discontinue or withdraw from the Treatment and Primary Follow-Up early will be asked to continue the study in the Secondary Follow-up Phase through Month 60.

7.1.3.2 Criteria for premature patient withdrawal from Treatment and Primary Follow-Up Phase

Patients must be followed according to the visit schedule for the Treatment and Primary Follow-Up to ensure adequate data are collected for the proper assessment of study primary and secondary objectives. It is strongly recommended that patients that remain in remission be followed in the Treatment and Primary Follow-Up Phase for at least one year at a minimum at the treating investigational site to ensure adequate safety and efficacy data collection. Patients may voluntarily withdraw from the Treatment and Primary Follow-Up Phase or be dropped from it at the discretion of the investigator at any time. It is anticipated that patients may leave the primary follow-up and move to Secondary Follow-Up due to reasons including:

- Treatment failure
- Relapse after remission
- Pursuing HSCT while in remission
- Patient voluntary withdrawal from the primary follow-up

For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

7.1.3.3 Relapse evaluation

If at any time during the Treatment and Primary Follow-Up phase following infusion, a patient who was in remission relapses, a full disease evaluation will be completed. As soon as possible after awareness of a relapse, the patient will be scheduled for a visit, and will have a bone marrow biopsy & aspirate, and peripheral blood collection. The following assessments will be performed:

a. Tumor characterization: Can be done on either blood or bone marrow with known tumor involvement of these components depending on availability of specimens, but priority is to do the majority of testing on bone marrow:
    - Flow cytometry (B and T cells, tumor cells and CD19 assessment)
    - Blood and bone marrow morphology
    - Cytogenetics/FISH
    - [redacted]
b. CTL019 cell characterization: Must be done on both peripheral blood and bone marrow, depending on availability of specimens:
    - PK by q-PCR and flow cytometry
    - Immunophenotyping by flow cytometry
c. Immunogenicity (humoral & cellular)
d. Bone Marrow Aspirate: exploratory [redacted] and mononuclear cell isolation. If bone marrow aspirate is not available, this analysis can

[redacted]

be performed on peripheral blood if tumor cells are present in the peripheral blood at relapse.

e. Physical Examination (including extramedullary disease assessment)

In the event of relapse due to extramedullary disease only, the patient may still be followed per the treatment and primary follow-up phase visit schedule until the institution of systemic antineoplastic therapy.

7.1.4 Secondary Follow-Up Phase

Patients who discontinue the Treatment and Primary Follow-Up Phase before month 60 will continue to be followed in the secondary follow-up phase in order to collect health authority requested data (e.g. delayed adverse events) up to 5 years after CTL019 infusion.

The first visit in the Secondary Follow-Up Phase is determined according to the time since CTL019 infusion when the patient discontinued from the Treatment and Primary Follow-Up Phase. For example, if the patient discontinue from the Treatment and Primary Follow-Up phase at Month 10, the first visit in the Secondary Follow-Up Phase will be Month 12.

During the secondary follow-up phase, patients may be monitored remotely by their health care provider or at the investigational site. Patients will undergo one or more of the following at each visit according to Table 7-2: Blood collection for hematology, CTL019 transgene persistence, flow cytometry (B and T cells) and RCL by VSV-G qPCR. In addition, patients will undergo a physical exam [including height, weight and Tanner staging (only for patients < 18 years old)]. If a patient still in remission cannot attend a regularly scheduled visit during the secondary follow-up, the investigator should attempt to determine relapse status and if the patient receives additional antineoplastic therapies at a minimum.

Adverse events and prior/concomitant medications will be maintained and assessed by the investigational site including emergence of new clinical conditions and mutagenic agents (cytotoxic drugs, radiation therapy, antineoplastic therapy, and stem cell transplant). If patient is monitored remotely, the investigator will request this information from the patient's health care provider.

Any pregnancies will be reported. Efficacy will be assessed in patients who are still in remission until relapse. For these patients, relapse status will be assessed at each visit per Table 7-2 and recorded in the clinical database.

For all patients who receive a CTL019 infusion, follow-up for survival every 3 months until end of study or enrolling into the long term follow-up, whichever comes first, is required. If a patient misses an annual scheduled visit where survival status is required, or if the time-point where survival status is required does not align with a scheduled visit, survival status can be obtained via phone contact with the patient or correspondence with local health care provider.

For details of assessments, refer to Table 7-2.

[redacted]

7.1.4.1 Adverse event and concomitant medication reporting during Secondary Follow-Up Phase

In order to monitor delayed adverse events per Health Authority guidance, selected adverse events/serious adverse events and concomitant medications will be recorded in the clinical database upon investigator knowledge as follows:

Adverse Events/Serious Adverse Events

- New incidence or exacerbation of a pre-existing neurological disorder
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- New incidence of other hematologic disorders
- Any severe adverse event or condition the investigator believes may have a reasonable relationship to CTL019 therapy
- Any severe adverse event or condition that is unexpected
- Positive RCL test result
- Vector insertion site sequencing result with a mono-or oligoclonality pattern or in a location near a known human oncogene
- New malignancy (T-cell & non T-cell), other than primary malignancy
- Progressive multifocal leukoencephalopathy (PML)
- Hepatitis B reactivation

Concomitant Medications

- Intravenous Immunoglobulin

Please refer to Appendix 4: CTL019 Modified Data Reporting – Secondary Follow Up Phase for reporting.

7.1.4.1.1 Serious adverse event definition

Serious adverse event (SAE) in the Secondary Follow Up phase is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent

[redacted]

  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event
- Positive RCL test result
- Vector insertion site sequencing result with a mono-or oligoclonality pattern or in a location near a known human oncogene
- New malignancy (T-cell & non T-cell), other than primary malignancy
- Progressive multifocal leukoencephalopathy (PML)
- Hepatitis B reactivation

7.1.4.2 Criteria for premature patient withdrawal from the study

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients lost to follow up should be recorded as such on the CRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

Patients may be withdrawn from the study if any of the following occur:

a. The patient is lost to follow-up
b. Patient noncompliance with study therapy and/or clinic appointments
c. Voluntary withdrawal; a patient may remove himself/herself from the study at any time without prejudice.
d. Termination of the study by the sponsor or the health authorities

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

7.1.5 Survival Follow-Up Phase

The survival phase intent is to collect survival data on patients that have completed the study. For all patients who complete the primary follow-up phase through 5 years, or complete the secondary follow-up phase through 5 years, additional follow-up will be made to determine survival every 3 months until end of study as defined in Section 4.2, or the patient is enrolled in the long term follow-up study, whichever occurs first. Survival status can be obtained via phone contact with the patient or correspondence with local health care provider.

7.1.6 Long-Term Follow Up

As a single administration study, patients are followed on study for 5 years post-infusion for safety and efficacy evaluations. A long term post-study follow-up for lentiviral vector safety will continue under a separate destination protocol. Patients will continue to be followed until 15 years post-CTL019 infusion per health authority guidelines.

[redacted]

Under the long term follow-up protocol, semiannual and annual evaluations will be performed on all patients who have received a CTL019 cell product infusion as recommended by the FDA and EMA in accordance with the relevant guidelines. All patients who either complete the study or prematurely discontinue post-CTL019 infusion will be automatically enrolled in this destination protocol at the time of study completion/discontinuation (separate informed consent/assent forms will be provided for this protocol). One to two times a year patients will visit the clinical site for a physical exam and medical history (including concomitant medications and adverse events) with careful attention to features possibly related to lentiviral associated events such as new malignancies, new incidence or exacerbation of a pre-existing neurologic disorder, new incidence or exacerbation of a prior rheumatologic or other autoimmune disorder, or new incidence of other hematologic disorders. In addition, labs will be drawn to evaluate routine safety endpoints, CTL019 vector persistence and RCL.

7.2 Assessment types

7.2.1 Efficacy assessments

Efficacy assessments will be performed according to the Novartis guidelines for efficacy evaluation in Acute Lymphoblastic Leukemia studies (Appendix 1), which is based on the NCCN version 1.2013 guidelines, Cheson et al (2003) and Appelbaum et al (2007).

An Independent Review Committee (IRC) appointed by Novartis will review data related to disease response assessment according to the Novartis guideline (Appendix 1). The IRC assessment will be used for the primary efficacy analysis. The local investigator assessments will be used for sensitivity analysis for select efficacy endpoints.

Table 7-3 Imaging or disease assessment collection plan – Primary Follow-up Phase

Procedure	Screening / Pre-infusion	Post-infusion Assessments
Bone marrow aspirate and biopsy for morphologic blast cell counts	Mandated	Mandated: Month 1 (Day 28). If patient is not in CR/CRi at Month 1, then required at the first time clinical evidence of remission is seen by peripheral blood and extramedullary disease assessment (physical exam and CNS symptoms) Recommended (but not required) at month 3 and 6 and as clinically indicated
Peripheral blood for morphologic blast, neutrophil and platelet cell counts	Mandated	Mandated: Months 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60 (EOT)
Lymph node or other involved tissue aspirate or biopsy	As clinically indicated	As clinically indicated
CSF Assessment/Lumbar puncture for CNS disease	Mandated	Mandated: Month 1 (Day 28). If patient is not in CR/CRi at Month 1, then required at the first time clinical evidence of remission is seen by peripheral blood and extramedullary disease assessment (physical exam and CNS symptoms) Additional CSF assessments as clinically indicated

[redacted]

Procedure	Screening / Pre-infusion	Post-infusion Assessments
MRD assessments (bone marrow aspirate)	Mandated	Mandated: Month 1 (Day 28). If patient is not in CR/CRi at Month 1, then required at the first time clinical evidence of remission is seen by peripheral blood and extramedullary disease assessment (physical exam and CNS symptoms) Recommended (but not required) at month 3 and 6 and as clinically indicated
CNS Brain Imaging (CT/MRI)	As clinically indicated	As clinically indicated
Extramedullary disease assessment (physical exam and CNS symptom assessment)	Mandated	Mandated: Months 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60 (EOT)
Flow Cytometry of peripheral blood (B and T cell, tumor cell, CD19 assessment)	Mandated	Mandated: Days 7, 14, and 21, and Months 1, 3, 6, 9, 12, 24, 36, 48 and 60 (EOT)

7.2.1.1 Physical examination

A targeted physical examination focusing upon sites of extramedullary disease involvement including assessments for hepatomegaly, splenomegaly, skin/gum infiltration, testicular masses and other disease manifestations are required. In addition, the physical examination will also include the assessments of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and the neurological system. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Significant findings that were present prior to the signing of informed consent/assent must be included in the **Medical History** page on the patient's CRF. Significant new findings that begin or worsen after informed consent/assent must be recorded on the Adverse Event page of the patient's CRF. For visits where disease response is assessed (month 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60), assessment results will be recorded on the physical exam disease response CRF page.

7.2.1.2 CNS symptom assessments

Assessment of patient reported symptoms suggestive of leukemic involvement of the CNS will be performed and recorded with each physical examination. Examples of CNS symptoms suggestive of leukemic involvement may include, but are not limited to, severe headache or nausea, meningismus or cognitive impairment, without other apparent etiologies. If clinical signs of CNS leukemia exist, it must be confirmed by CNS imaging (CT or MRI of brain) or other relevant methods (e.g. biopsy, LP, etc.) to define CNS relapse. For visits where disease response is assessed (month 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60), assessment results will be recorded on the CNS disease response CRF page.

7.2.2 Safety and tolerability assessments

Safety will be monitored by physical examination, assessing immunogenicity against CTL019, lab abnormalities as well as collecting adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

[redacted]

Tanner staging for patients less than 18 years of age will be updated semiannually in the treatment and primary follow-up phase, and annually in the secondary follow-up phase. If a patient is classified as Tanner Stage 5 at screening or at any point during the trial, no further Tanner staging will be required for the remainder of the trial. Female patient reproductive status (menstrual status and pregnancy information) will be updated monthly from month 2 through 6, then quarterly through two years, then semiannually thereafter during the primary follow-up phase. Female patient reproductive status will be updated annually in the secondary follow-up phase.

7.2.2.1 Vital signs

Vital signs include temperature, blood pressure, pulse measurements, respiratory rate, and pulse oxygen.

7.2.2.2 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing will be measured via a consistent method at each assessment.

7.2.2.3 Performance status

Table 7-4 Karnofsky/Lansky Performance Scales

Karnofsky Scale (age ≥ 16 years)		**Lansky Scale (age < 16 years)**	
Able to carry on normal activity and to work; no special care needed.		Able to carry on normal activity; no special care is needed	
100	Normal no complaints; no evidence of disease	**100**	Fully active
90	Able to carry on normal activity; minor signs or symptoms of disease	**90**	Minor restriction in physically strenuous play
80	Normal activity with effort; some signs or symptoms of disease	**80**	Restricted in strenuous play, tires more easily, otherwise active
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.		Mild to moderate restriction	
70	Cares for self; unable to carry on normal activity or to do active work	**70**	Both greater restrictions of, and less time spent in active play
60	Requires occasional assistance, but is able to care for most of his personal needs	**60**	Ambulatory up to 50% of the time, limited active play with assistance/supervision
50	Requires considerable assistance and frequent medical care	**50**	Considerable assistance required for any active play, fully able to engage in quiet play
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.		Moderate to severe restriction	
40	Disabled; requires special care and assistance	**40**	Able to initiate quiet activities
30	Severely disabled; hospital admission is indicated although death not imminent	**30**	Needs considerable assistance for quiet activity
20	Very sick; hospital admission necessary; active supportive treatment necessary	**20**	Limited to very passive activity initiated by others (e.g. television)
10	Moribund; fatal processes progressing rapidly	**10**	Completely disabled, not even passive play
0	Dead	**0**	Unresponsive

[redacted]

7.2.2.4 Tanner staging (only for patients < 18 years old)

7.2.2.4.1 Males

Genitalia stages:

Stage 1: Pre-adolescent. Testes, scrotum, and penis are of about the same size and proportion as in early childhood.

Stage 2: The scrotum and testes have enlarged and there is a change in the texture of the scrotal skin. There is also some reddening of the scrotal skin.

Stage 3: Growth of the penis has occurred, at first mainly in length but with some increase in breadth. There has been further growth of testes and scrotum.

Stage 4: Penis further enlarged in length and breadth with development of glans. Testes and scrotum further enlarged. There is also further darkening of the scrotal skin.

Stage 5: Genitalia adult in size and shape. No further enlargement takes place after Stage 5 is reached.

Pubic hair stages:

Stage 1: Pre-adolescent. The velus over the pubesis no further developed than that over the abdominal wall, i.e. no pubic hair.

Stage 2: Sparse growth of long, slightly pigmented, downy hair, straight or only slightly curled, appearing chiefly at the base of the penis.

Stage 3: Considerably darker, coarser, and more curled. The hair spreads sparsely over the junction of the pubes.

Stage 4: Hair is now adult in type, but the area covered by it is still considerably smaller than in most adults. There is no spread to the medial surface of the thighs.

Stage 5: Hair distribution is adult in quantity and type and is described in the inverse triangle. Hair can be spread to the medial surface of the thighs.

7.2.2.4.2 Females

Breast stages:

Stage 1: Pre-adolescent; elevation of papilla only.

Stage 2: Breast bud stage; elevation of breast and papilla as a small mound, enlargement of areola diameter.

Stage 3: Further enlargement of breast and areola, with no separation of their contours.

Stage 4: Projection of areola and papilla to form a secondary mound above the level of the breast.

Stage 5: Mature stage; projection of papilla only, due to recession of the areola to the general contour of the breast.

[redacted]

Pubic hair stages:

Stage 1: Pre-adolescent; the vellus over the pubes is not further developed than that over the anterior abdominal wall, i.e. no pubic hair.

Stage 2. Sparse growth of long, slightly pigmented, downy hair, straight or only slightly curled, appearing chiefly along the labia.

Stage 3: Considerably darker, coarser, and more curled. The hair spreads sparsely over the junction of the pubes.

Stage 4: Hair is now adult in type, but the area covered by it is still considerably smaller than in most adults. There is no spread to the medial surface of the thighs.

Stage 5: Adult in quantity and type, distributed as an inverse triangle of the classically feminine pattern. Spread to the medial surface of the thighs, but not up the linea alba or elsewhere above the base of the inverse triangle.

7.2.2.5 Laboratory evaluations

Screening and other laboratory assessments will be performed accordingly to Table 7-1 and Table 7-2. Note: Additional assessments should be performed between visits as clinically required to follow AEs or CTL019 expected events and for detailed modified data capture for inpatient/in hospital events, refer to Section 8.1.1. For all laboratory assessments that occur on Day 1, these should be performed prior to CTL019 infusion unless indicated otherwise.

The Investigator will evaluate the clinical significance of each applicable laboratory value outside of the reference range. This decision shall be based upon the nature and degree of the observed abnormality. Values which are considered clinically significant and/or study related to CTL019 will be noted. The Investigator may choose to repeat any abnormal result, in order to rule out laboratory error.

With respect to laboratory assessments listed within this protocol, please refer to the [Laboratory Manual] for further guidance on prioritizing sample acquisition when patient blood volume collection limitations exist.

[redacted]

Table 7-5 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Mean Corpuscular Hemoglobin Concentration (MCHC), MCV (Mean Corpuscular Volume), Platelets, Red blood cells, White blood cells with complete differential (Basophils, Eosinophils, Lymphocytes, Atypical Lymphocytes, Monocytes, Neutrophils, Lymphoblasts, Plasma cells, Prolymphocytes, Myelocytes, Metamyelocytes, and Promyelocytes)
Chemistry	Glucose (fasting or non-fasting), Blood Urea Nitrogen (BUN) or Urea, Creatinine, Sodium, Potassium, Calcium, Total Protein, Albumin, Total Bilirubin, Alkaline Phosphatase, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Magnesium, Phosphorus, Lactate Dehydrogenase (LDH), Ferritin, C-reactive Protein (CRP) and Uric Acid.
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity) If macroscopic panel is abnormal then perform microscopic panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation	Prothrombin time (PT) or International normalized ratio (INR), activated Partial thromboplastin time (aPTT), fibrinogen, and D-dimer
Pregnancy screen	Serum or urine tests
Viral Serology	Rapid Influenza A & B, Hepatitis C Virus (HCV) RNA qualitative test or antibody, Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (anti-HBc), Hepatitis B surface antibody (anti-HBs), HIV (if an initial HIV screening test is positive then a confirmatory HIV test is required to be performed as per current local guidelines)
CSF	White Blood Cells, Presence or absence of lymphoblasts, Red Blood cells, Glucose, Protein
Additional assessments	Serum immunoglobulin levels (IgG, IgA, IgM), peripheral blood, donor chimerism (prior allogeneic SCT patients only, or if unknown), bone marrow morphologic blast cell counts, peripheral blood morphologic blast, neutrophil and platelet cell counts

Table 7-6 Central clinical laboratory parameters collection plan

Test Category	Test Name
MRD	MRD flow panel (bone marrow aspirate), B cells, CD19 assessment
Flow cytometry & Blood MRD (treatment and primary follow-up)	B cells, tumor cell immunophenotyping, CD19 assessment
Flow cytometry (secondary follow-up)	Peripheral blood B and T cells
[redacted]	[redacted]
CTL019 assessments (includes T cells)	CTL019 PK by q-PCR and/or flow cytometry (peripheral blood and bone marrow aspirate), CTL019 immunophenotyping by flow cytometry (peripheral blood)
Cytokines	Serum cytokine panel (peripheral blood)
RCL (VSV-G)	VSV-g q-PCR (peripheral blood)
Immunogenicity	Prevalence and Incidence of immunogenicity against CTL019 (peripheral blood and serum)
[redacted]	[redacted]

Refer to the [Laboratory Manual] for more detailed instructions for the collection, handling, and shipment of PK and biomarker samples.

[redacted]

7.2.3 Pharmacokinetics

Table 7-7 CTL019 pharmacokinetics by q-PCR in peripheral blood collection log

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume**
1	W-16 to D-1 Enrollment/Pre-Chemotherapy	3 mL
1	D1 10 min ± 5 min post-infusion	3 mL
1	D4±1d	3 mL
1	D7±1d	3 mL
1	D11 ±1d	3 mL
1	D14±3d	3 mL
1	D21±3d	3 mL
1	D28±4d	3 mL
1	M3±14d	3 mL
1	M6±14d	3 mL
1	M9±14d	3 mL
1	M12±14d	3 mL
1	M18±14d	3 mL
1	M24±14d	3 mL
1	M30±14d	3 mL
1	M36±14d	3 mL
1	M42±14d	3 mL
1	M48±14d	3 mL
1	M54±14d	3 mL
1	M60±14d (EOT)	3 mL
1	Unscheduled (PK samples related to CRS)***	2 mL/collection
1	Unscheduled (PK samples at relapse)****	3 mL
1	Unscheduled (PK samples related to safety events)	3 mL/collection

*All measurement times are relative to date of CTL019 infusion unless otherwise specified.

**All patient sample volumes subject to adjustment for size and patient condition.

*** Additional unscheduled samples may be collected as needed dependent upon individual patient differences in the clinical time-course of CRS and administration of anti-cytokine therapy, if clinically feasible. Unscheduled PK sample collections related to CRS will cease once PK sample collections related to anti-cytokine therapy commence, if applicable.

**** In the event patient relapses, an unscheduled PK sample should be collected along with corresponding immunogenicity sample (refer to Table 7-13)

Note: [redacted] is performed from these same samples (refer to Table 7-17). RCL by VSVg qPCR is performed at the relevant time points using DNA extracted from these samples.

[redacted]

Table 7-8 CTL019 pharmacokinetics by flow cytometry in peripheral blood collection log

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume
1	W-16 to D-1 Enrollment/Pre-Chemotherapy	2 mL
1	D4±1d	2 mL
1	D7±1d	2 mL
1	D11 ±1d	2 mL
1	D14±3d	2 mL
1	D21±3d	2 mL
1	D28±4d	2 mL
1	M3±14d	2 mL
1	M6±14d	2 mL
1	M9±14d	2 mL
1	M12±14d	2 mL
1	M18±14d	2 mL
1	M24±14d	2 mL
1	M30±14d	2 mL
1	M36±14d	2 mL
1	M42±14d	2 mL
1	M48±14d	2 mL
1	M54±14d	2 mL
1	M60±14d (EOT)	2 mL
1	Unscheduled (PK samples related to CRS)**	2 mL/collection
1	Unscheduled (PK sample at relapse)***	
1	Unscheduled (e.g. related to safety events)	2 mL

*All measurement times are relative to date of CTL019 infusion unless otherwise specified.

** Additional unscheduled samples may be collected as needed dependent upon individual patient differences in the clinical time-course of CRS, if clinically feasible.

***In the event patient relapses, an unscheduled PK sample should be collected along with corresponding immunogenicity sample (refer to Table 7-13 and Table 7-14)

Table 7-9 CTL019 pharmacokinetics by q-PCR in bone marrow aspirate collection log

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume**
1	W-16 to W-12 Screening	2 mL
1	D28±4d	2 mL
1	M3±14d (recommended but not required)	2 mL
1	M6±14d (recommended but not required)	2 mL
1	Unscheduled (PK sample at relapse)	2 mL
1	Unscheduled (e.g. related to safety events)	2 mL/collection

*All measurement times are relative to date of CTL019 infusion unless otherwise specified.

**All patient sample volumes subject to adjustment for size and patient condition.

Note: [redacted] is performed from these same samples; refer to Table 7-17.

[redacted]

Table 7-10 CTL019 pharmacokinetics by flow cytometry in bone marrow aspirate collection log

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume**
1	W-16 to W-12 Screening	2 mL
1	D28±4d	2 mL
1	M3±14d (recommended but not required)	2 mL
1	M6±14d (recommended but not required)	2 mL
1	Unscheduled (PK sample at relapse)	2 mL
1	Unscheduled (e.g. related to safety events, at relapse)	2 mL/collection

*All measurement times are relative to date of CTL019 infusion unless otherwise specified.

Table 7-11 CTL019 pharmacokinetics by q-PCR in CSF collection log

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume
1	W-16 to W-12 Screening	4-6 mL
1	D28±4d	4-6 mL
1	Unscheduled	4-6 mL/collection

*All measurement times are relative to date of CTL019 infusion unless otherwise specified.

Table 7-12 CTL019 transgene persistence in peripheral blood (for patients in Secondary Follow-up)

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume
1	M3±14d	3 mL
1	M6±14d	3 mL
1	M9±14d	3 mL
1	M12±14d	3 mL
1	M24±14d	3 mL
1	M36±14d	3 mL
1	M48±14d	3 mL
1	M60±14d	3 mL
1	Unscheduled (at relapse)**	3 mL
1	Unscheduled (e.g. related to safety events, at relapse)	3 mL

*All measurement times are relative to date of CTL019 infusion unless otherwise specified.

Note: RCL by VSVg qPCR is performed at the relevant timepoints using DNA extracted from these samples.

**In the event patient relapses, an unscheduled PK sample should be collected along with corresponding immunogenicity sample (refer to Table 7-13 and Table 7-14)

[redacted]

Table 7-13 Immunogenicity serum sample collection log

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume**
1	W-16 to D-1 Enrollment/Pre-Chemotherapy	5 mL
1	D14±3d	5 mL
1	D28±4d	5 mL
1	M3±14d	5 mL
1	M6±14d	5 mL
1	M12±14d	5 mL
1	Unscheduled (at relapse)***	5 mL
1	Unscheduled (e.g. related to safety events)	5 mL/collection

*All measurement times are relative to date of CTL019 infusion unless otherwise specified.
**Aliquot obtained from serum cytokine collection; refer to Table 7-17.
*** In the event patient relapses, an unscheduled immunogenicity sample should be collected along with corresponding PK samples (refer to Table 7-7, Table 7-8, and Table 7-12)

Table 7-14 Immunogenicity peripheral blood sample collection log

Treatment Period or Cycle	Day/ Scheduled Time Point*	Sample Volume**
1	W-16 to D-1 Enrollment/Pre-Chemotherapy	10 mL
1	D14±3d	10 mL
1	D28±4d	10 mL
1	M3±14d	10 mL
1	M6±14d	10 mL
1	M12±14d	10 mL
1	Unscheduled (at relapse)***	10 mL
1	Unscheduled (e.g. related to safety events)	10 mL/collection

*All measurement times are relative to date of CTL019 infusion unless otherwise specified
**All patient sample volumes subject to adjustment for size and patient condition.
Note: Immunophenotyping (peripheral blood) is performed from these same samples; refer to Table 7-17.
*** In the event patient relapses, an unscheduled immunogenicity sample should be collected along with corresponding PK sample (refer to Table 7-7, Table 7-8, and Table 7-12)

[redacted]

Table 7-15 Tocilizumab pharmacokinetics (PK), CTL019 PK and sIL6R (PD) in tocilizumab treated patients during CRS

Day/ Scheduled Time Point*/**	Dose Reference ID	Tocilizumab Sample Number	Sample Volume (serum) (PK+PD)	CTL019 PK by qPCR Sample Number	Sample Volume (whole blood)	CTL019 PK by flow cytometry Sample Number	Sample Volume (whole blood)
D1 (5-15 minutes post infusion)	101	1	5 mL	--	--	--	--
D1 1 hour ± 15 min post infusion	101	2	5 mL	201	2 mL	601	2 mL
D2 ± 2 hours	101	3	5 mL	202	2 mL	602	2 mL
D3 ± 4 hours	101	4	5 mL	203	2 mL	603	2 mL
D7 ± 1d	101	5	5 mL	204	2 mL	604	2 mL
D1 (pre-dose; second infusion)	101	6	5 mL	205	2 mL	605	2 mL
D1(5-15 minutes post second infusion)	102	7	5 mL	--	--	--	--
D2 ± 2 hours from second infusion	102	8	5 mL	206	2 mL	606	2 mL
D3 ± 4 hours	102	9	5 mL	207	2 mL	607	2 mL
D7 ± 1d	102	10	5 mL	208	2 mL	608	2 mL
D1 (5-15 minutes pre-dose; additional infusion)	102	11	5 mL	209	2 mL	609	2 mL
D1 (5- 15 minutes post additional infusion	103	12	5 mL	--	--	--	--
D2 ± 2 hours	103	13	5 mL	210	2 mL	610	2 mL
D3 ± 4 hours	103	14	5 mL	211	2 mL	611	2 mL
D7 ± 1d	103	15	5 mL	212	2 mL	612	2 mL
Additional ***	104, 105	16, 17, 18, 19, 20	5 mL	213, 214, 215, 216	2 mL	613, 614, 615, 616	2 mL

*All measurement times are relative to tocilizumab infusion unless otherwise specified. A serum sample collected at D1 for cytokine analysis (see Table 7-17) would serve as the baseline sample.

**Samples may be collected as needed dependent upon administration of tocilizumab, if clinically feasible.

Unscheduled CTL019 PK sample collections related to CRS as specified in Table 7-7, Table 7-8, and Table 7-17 will cease once PK/PD sample collections related to tocilizumab infusion commence, if applicable.

*** Additional PK samples collected in the event more than 2 tocilizumab doses are administered should follow additional PK collection and numbering schedule.

[redacted]

Table 7-16 Siltuximab PK, CTL019 PK and sIL6R (PD) in siltuximab treated patients during CRS

Day/ Scheduled Time Point*/**	Dose Reference ID	Siltuximab Sample Number	Sample Volume (serum) (PK+PD)	CTL019 PK by qPCR Sample Number	Sample Volume (whole blood)	CTL019 PK by flow cytometry Sample Number	Sample Volume (whole blood)
D1 (5-15 minutes post infusion)	301	401	5 mL	--	--	--	--
D1 1 hour ± 15 min post infusion	301	402	5 mL	501	2 mL	701	2 mL
D2 ± 2 hours	301	403	5 mL	502	2 mL	702	2 mL
D3 ± 4 hours	301	404	5 mL	503	2 mL	703	2 mL
D7 ± 1d	301	405	5 mL	504	2 mL	704	2 mL
D1 (pre-dose; additional infusion)	301	406	5 mL	505	2 mL	705	2 mL
D1(5-15 minutes post additional infusion)	302	407	5 mL	--	--	--	--
D2 ± 2 hours from additional infusion	302	408	5 mL	506	2 mL	706	2 mL
D3 ± 4 hours	302	409	5 mL	507	2 mL	707	2 mL
D7 ± 1d	302	410	5 mL	508	2 mL	708	2 mL
Additional***	303, 304	411, 412, 413, 414, 415	5 mL	509, 510, 511, 512	2 mL	709,710, 711, 712	2 mL

*All measurement times are relative to siltuximab administration unless otherwise specified. A serum sample collected at D1 for cytokine analysis (see Table 7-17) would serve as the baseline sample.

**Samples may be collected as needed dependent upon administration of siltuximab, if clinically feasible. Unscheduled CTL019 PK sample collections related to CRS as specified in Table 7-7, Table 7-8, and Table 7-17 will cease once PK/PD sample collections related to siltuximab administration commence, if applicable.

*** Additional PK samples collected in the event more than 1 siltuximab dose is administered should follow additional PK collection and numbering schedule.

7.2.3.1 Analytical method

The assays to be utilized for various PK/biomarker assessments [redacted] in peripheral blood and other tissues and flow cytometric analysis to detect CTL019 positive cells. Details regarding collection and processing of the samples used in these assays will be provided in the Central Laboratory Manual.

7.2.4 Biomarkers

The plan for biomarker evaluation focuses on characterization of CTL019 cellular pharmacokinetics (see Section 10.5.4), serum cytokines temporally linked to CRS, clonal changes in ALL tumor cells and enumeration of normal B cell levels.

[redacted]

The assessment of CTL019 cellular kinetics measures the percent of peripheral blood mononuclear cells expressing the CTL019 transgene and the relative percentage of other T cell subsets that express the CTL019 transgene protein. [redacted] These measurements will be used to explore the possible relationships between the relative number of peripheral blood mononuclear cells expressing CTL019 and safety or efficacy outcomes. In parallel, the serum level of inflammatory or immune cytokines will be assessed post-CTL019 administration. These data will be used to retrospectively identify candidate predictive serum markers of CTL019 efficacy and severity of CRS. Finally, the relationship between tumor cell target expression (CD19) and efficacy in addition to the effect of CTL019 on ALL clonal evolution will also be assessed. [redacted] This assessment will determine if CTL019 eliminates all detectable malignant clones or whether a particular clonal variant is resistant to CTL019 elimination. Additionally, this methodology provides information about the clonal evolution of IGH sequences. In total, [redacted] The effect of CTL019 therapy on normal B cell levels will be measured in peripheral blood and bone marrow aspirate to assess the on-target effect on these CD19 positive cells.

[redacted] Comprehensive DNA sequencing is within scope of these analyses (in accordance with local regulations); at a minimum, targeted sequencing of genes relevant to the CTL019 mechanism of action will be conducted. Finally, bone marrow mononuclear cells will be used to explore the correlation between genetics, epigenetics and outcome.

[redacted]

Table 7-17 Biomarker sample collection plan

Day/ Scheduled Time Point*	Sample Volume**
Peripheral blood for serum cytokine analyses	
W-16 to D-1 Enrollment/Pre-Chemotherapy	5 mL
D1 (pre-infusion)	10 mL
D2	5 mL
D4±1d	5 mL
D7±1d	5 mL
D14±3d	5 mL
D21±3d	5 mL
D28±4d	5 mL
M3±14d	5 mL
M6±14d	5 mL
M12±14d	5 mL
Unscheduled (PD samples related to CRS)***	5 mL/collection
*All measurement times are relative to date of CTL019 infusion unless otherwise specified.	
**All patient sample volumes subject to adjustment for size and patient condition.	
*** Additional unscheduled samples may be collected as needed dependent upon individual patient differences in the clinical time-course of CRS and should be consistent with timing of unscheduled PK in Table 7-15 and Table 7-16, if clinically feasible. Please note that results of cytokine analyses are NOT to be used for clinical management decisions of CRS. Unscheduled PK/PD sample collections related to CRS will cease once PK/PD sample collections related to anti-cytokine therapy as specified in Table 7-15 and Table 7-16 commence, if applicable.	
[redacted]	
W-16 to D-1 Enrollment/Pre-Chemotherapy	3 mL
D28±4d	3 mL
M3±14d	3 mL
M6±14d	3 mL
M12±14d	3 mL
*All measurement times are relative to date of CTL019 infusion unless otherwise specified.	
*Aliquot obtained from CTL019 peripheral blood q-PCR sample as specified in Table 7-7.	
[redacted]	
W-16 to W-12 Screening	2 mL
D28±4d	2 mL
M3±14d (recommended but not required)	2 mL
M6±14d (recommended but not required)	2 mL
*All measurement times are relative to date of CTL019 infusion unless otherwise specified.	
*Aliquot obtained from CTL019 bone marrow q-PCR aspirate as specified in Table 7-9.	

[redacted]

Day/ Scheduled Time Point*	Sample Volume**
CTL019 Immunophenotyping (peripheral blood)	
W-16 to D-1 Enrollment/Pre-Chemotherapy	10 mL
D7±1d	10 mL
D14±3d	10 mL
D21±3d	10 mL
D28±4d	10 mL
M3±14d (Primary follow-up only)	10 mL
M6±14d (Primary follow-up only)	10 mL
M9±14d (Primary follow-up only)	10 mL
M12±14d (Primary follow-up only)	10 mL
M24±14d (Primary follow-up only)	10 mL
M36±14d (Primary follow-up only)	10 mL
Unscheduled (related to relapse)	10 mL
*All measurement times are relative to date of CTL019 infusion unless otherwise specified. ** Except for collections at M24 and M36, aliquot obtained from peripheral blood immunogenicity assay as specified in Table 7-14.	
Bone marrow [redacted]	
W-16 to W-12 Screening	2 mL
Unscheduled (e.g. related to relapse)	2 mL
Bone marrow genomic analysis (mononuclear cells)	
W-16 to W-12 Screening	4 mL
Unscheduled (e.g. related to relapse)	4 mL

7.2.5 Optional additional exploratory assessments using remaining samples

If the patient agrees, the remaining biomarker and/or PK samples as well as any CTL019 manufactured product that is not infused may be stored for up to 15 years and further analyzed to address scientific questions related to CTL019 or cancer, including research related to improvements or enhancements in the manufacturing process. A decision to perform such additional research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

7.2.6 Resource utilization

Hospitalizations will be evaluated in this study as an exploratory endpoint to characterize the impact of study treatment on this aspect of healthcare resource utilization. In addition, these data may be used to support assessments used to characterize the economic impact of study treatment regimens.

Healthcare resource utilization data regarding hospitalizations should be captured from the day of screening up to Month 2 for the patient as described in Table 7-1.

Hospitalizations as a result of the following reasons are not to be reported:

- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

[redacted]

- Treatments occurring on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE as described in Section 8.2.1 are not required.

Information related to the length of stay (e.g., dates of admission or discharge), hospital ward facilities used (e.g., emergency department, intensive care unit, general ward, etc.), reasons for hospitalization as associated with the study treatment regimen, disease and/or disease progression, or any other reason will be of interest; and hospital discharge information will be evaluated.

7.2.7 Patient reported outcomes

Two questionnaires will be used in this study to capture patient reported outcomes (PROs): PedsQL and EQ-5D. PedsQL™ will be completed by patients aged 8 and above, and EQ-5D will be completed by patients aged 8 and above. Brief description and administration guidelines for each questionnaire are given in the sections below.

The patient should be given the questionnaire(s) and completed at the scheduled visit before the patient sees the investigator or undergoes other clinical assessments. However, for the enrollment visit where the interaction between the physician and the patient cannot be avoided, questionnaire(s) can be completed before or after seeing the investigator. Under extenuating circumstances where the enrollment (baseline) questionnaire(s) was not completed at the enrollment visit, it must be completed before administration of LD chemotherapy or the CTL019 infusion if LD chemotherapy is not administered. Questionnaires should be completed in the language the respondent is most familiar with. The patient should be given sufficient space and time to complete the questionnaire.

The study coordinator should check the questionnaire for completeness and encourage the patient to complete any missing responses. The original questionnaire will be kept with the patient's file as the source document. Detailed instructions relating to the administrative procedures of the questionnaires will be provided to the sites. Patient's refusal to complete all or any part of a questionnaire should be documented in the study data capture system.

Discourage the parent, child, or other family members from consulting with one another during the completion of the questionnaire. Let them know that they can feel free to discuss their answers following completion of the questionnaires.

If the child or parent has a question about what an item means or how they should answer it, do not interpret the question for them. Repeat the item to them verbatim. Ask them to answer the item according to what they think the question means. If they have trouble deciding on an answer, ask them to choose the response that comes closest to how they feel. The child has the option of not answering a question if they truly do not understand the question.

Completed questionnaire(s) and any unsolicited comments written by the patient should be reviewed and assessed by the investigator for responses which may indicate potential AEs, including SAEs, before any clinical study assessments. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the patient to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 8.

[redacted]

7.2.7.1 Pediatric Quality of Life Inventory – Version 4 (PedsQL™ 4.0)

The PedsQL is a generic instrument that is commonly used to measure health related quality of life (HRQL) in children and youth aged 0-25. The instrument is available for different age groups and consist of 23 items covering four dimensions of HRQL: Physical functioning, Emotional functioning, Social functioning, and School functioning. The questionnaire requires approximately 5 to 10 minutes to complete.

In this study the following versions of PedsQL will be administered to patients ages of 8 and above:

- PedsQL™ 4.0 (Adult) for patients aged 18 and above at study entry
- PedsQL™ 4.0 (Teens) for patients between the ages of 13-17 at study entry
- PedsQL™ 4.0 (Children) for patients between the ages of 8-12 at study entry

Children (8-12) and Teens (13-18) may self-administer the PedsQL™ after introductory instructions from the administrator. If the administrator determines that the child or teen is unable to self-administer the PedsQL™ (e.g., due to illness, fatigue, reading difficulties), the PedsQL™ should be read aloud to the child or teen.

If a child has difficulty understanding the age-appropriate PedsQL™, the preceding age group version may be administered to the child. Since the PedsQL Young Child questionnaire (for ages 5-7) will not be utilized in this trial, a patient in the 8-12 year old age group with difficulty understanding will therefore not complete a PedsQL questionnaire.

7.2.7.2 EuroQol EQ-5D (EQ-5D)

The EQ-5D is a widely used, self-administered questionnaire designed to assess health status in adults, however, later studies have demonstrated acceptable performance in adolescents aged 12 to 18 years. A child-friendly version, the EQ5DY, has been developed for use in children aged 8 years and older (Wille et al 2010).

The measure is divided into two distinct sections. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression).

Patients rate each of these items from “no problem,” “some problem,” or “extreme problem.” A composite health index is then defined by combining the levels for each dimension. The second section of the questionnaire measures self-rated (global) health status utilizing a vertically oriented visual analogue scale where 100 represents the “best possible health state” and 0 represents the “worst possible health state.” Respondents are asked to rate their current health by placing a mark along this continuum. The recall period is “today,” and the questionnaire requires approximately 5 to 10 minutes to complete.

In this study the following versions of EQ-5D will be used:

- EQ-5D for patients aged 13 and above at study entry
- EQ-5D-Y for patients between the ages of 8 and 12 at study entry.

7.2.7.3 Questionnaire administration

Completion of the following questionnaire(s) will be required based on age at study entry:

[redacted]

Age at study entry	PedsQL™ V4 Version	EQ-5D Version
2-4	Not Done	Not Done
5-7	Not Done	Not Done
8-12	PedsQL (Children)	EQ-5D-Y
13-17	PedsQL (Teen)	EQ-5D
18+	PedsQL (Adult)	EQ-5D

Please refer to the Guidelines for administering the PRO questionnaires for further instruction. If a child has difficulty understanding the age-appropriate questionnaire version, the preceding age group version may be administered to the child, if available. If a translated language is not available for the local country language(s) or a patient's native language, questionnaire completion is not required.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent/assent has been obtained.

Abnormal laboratory values or test results occurring after informed consent/assent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

8.1.2 Reporting

Adverse events that begin or worsen after informed consent/assent will be recorded in the patient's source documents. New or worsening adverse events **prior to starting study treatment** (i.e. lymphodepleting chemotherapy or the pre-infusion visit if the lymphodepleting chemotherapy is not given per Section 6.1.1.1) are required to be recorded in the Adverse Events CRF if they meet one of the following criteria:

- All infections
- All clinical AEs grade ≥ 3
- All laboratory abnormalities deemed clinically significant by the investigator
- All AEs related to a study procedure
- All AEs leading to study discontinuation
- All SAEs meeting criteria outlined in Section 8.2.2.

Under the circumstance when a patient is simultaneously enrolled in the active phase (up to Day 2) of the Novartis CTL019B2206 leukapheresis (apheresis collection) protocol and this treatment protocol, collection and reporting of adverse events during this overlapping period should follow the CTL019B2206 safety reporting criteria.

[redacted]

Once the patient begins lymphodepleting chemotherapy or the pre-infusion visit, all new or worsening adverse events, including laboratory abnormalities deemed clinically significant by the investigator, will be recorded in the Adverse Events CRF up to the Month 12 visit.

Adverse event monitoring should be continued through the Month 60 (EOT) visit. **Following the Month 12 visit, and through the Month 60 visit**, adverse events should only be reported to Novartis and recorded in the Adverse Events CRF if it meets one of the following criteria:

- Events leading to death
- Events related to a study procedure
- Infections:
  - Serious or opportunistic infections. Defined as bacterial, viral, fungal or parasitic infections that fulfill one of the following criteria:
    - Require anti-infective treatment OR
    - Lead to significant disability or hospitalization OR
    - Need for surgical or other intervention
- New incidence or exacerbation of a pre-existing neurologic disorder
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- New incidence of other hematologic disorder
- Any severe adverse event or condition the investigator believes may have a reasonable relationship to CD19 CART therapy
- Positive RCL test result
- Vector insertion site sequencing result with a mono-or oligoclonality pattern or in a location near a known human oncogene
- New malignancy (T-cell & non T-cell), other than the primary malignancy
- Progressive multifocal leucoencephalopathy (PML)
- Hepatitis B reactivation

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Medical Dictionary for Regulatory Authorities (MedDRA) and the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, with the exception of CRS, which will follow Table 6-1. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study but is collected as a seriousness criteria; rather, information about deaths will be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient during the screening process after signing informed consent/assent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during

[redacted]

the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE v. 4.03 Grade 1-4)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, temporarily interrupted, permanently discontinued, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
7. Whether it is serious, where a serious adverse event is defined as in Section 8.2.1 and which seriousness criteria have been met.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of primary study indication (including fatal outcomes), if documented by use of appropriate method, should not be reported as an adverse event.

Modified data capture for inpatient/in hospital events

A significant number of CTL019 treated patients will require multiple days of inpatient and/or ICU care. These adverse events are mostly due to CRS and MAS, although there may be some contribution from the preceding lymphodepleting chemotherapy (neutropenia fever, cytopenias). CRS/MAS toxicity is an ‘on-target’ effect resulting from the expected CTL019 cell expansion, activation and tumor cell killing.

A typical inpatient or ICU day can generate hundreds of data points and many therapeutic dose changes throughout a given day. These inpatient events and days are not scheduled protocol defined visits although they are anticipated to occur in some patients. A revised inpatient data capture will be utilized for this study to systematically collect subsets of patient data to describe the management of safety events associated with CTL019 therapy for the purpose of:

1. Adequately informing physicians and patients of the expected risks of CTL019 and the recommended interventions to manage these risks
2. Health authority submission

This is done through a targeted collection of concomitant medications and laboratory data and CRS CRFs specifically designed to capture CTL019-related toxicity, severity, interventions

[redacted]

and response/resolution following intervention. Details can be found in the CRF Completion Guidelines (CCGs).

8.1.3 Laboratory test abnormalities

8.1.3.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities that do not meet the definition of an adverse event should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.4 Adverse events of special interest

Adverse events of special interest (AESI) are described in Table 10-3. The current search criteria of AESI are based on limited experience from ongoing clinical studies without an accurate assessment of causality. The search criteria of the AESI may be updated prior to database lock for primary analysis reporting. Based on current clinical experience, AESI typically occur and resolve within 8 weeks of CTL019 infusion in ALL patients.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition

[redacted]

  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent/assent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

Any SAEs experienced during the screening/pre-treatment phase (from the time of patient providing informed consent/assent until the patient begins study-related treatment) should ONLY be reported to Novartis and be captured if the CRF and safety database if the event meets at least one of the following criteria:

- All events leading to death.
- All pulmonary or cardiac abnormalities
- All infections
- All events related to a study procedure
- Any AE reportable for this study period that also meets criteria for serious
- Any substantial change in the status of the patient that precludes the patient from proceeding to study treatment (e.g. GVHD, rapid progression of malignancy, marked decline in performance status)
- Any other substantial change in the clinical status of the patient that the investigator deems may have a potential impact on the patients during lymphodepletion and CTL019 treatment

Under the circumstance when a patient is simultaneously enrolled in the active phase (up to Day 2) of the Novartis CTL019B2206 leukapheresis (apheresis collection) protocol and this treatment protocol, collection and reporting of serious adverse events during this overlapping period should follow the CTL019B2206 safety reporting criteria.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has begun study-related treatment (i.e. lymphodepleting chemotherapy, or pre-CTL019 infusion visit if no lymphodepleting chemotherapy was given) and through the Month 12 visit must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after the Month 12 visit, and through the Month 60 (EOT) visit should only be reported to Novartis and recorded in the Adverse Events CRF if it meets one of the following criteria:

- Events leading to death
- Events related to a study procedure
- Infections:
  - Serious or opportunistic infections. Defined as bacterial, viral, fungal or parasitic infections that fulfill one of the following criteria:

[redacted]

  - Require anti-infective treatment OR
  - Lead to significant disability or hospitalization OR
  - Need for surgical or other intervention
- New incidence or exacerbation of a pre-existing neurologic disorder
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- New incidence of other hematologic disorder
- Any severe adverse event or condition the investigator believes may have a reasonable relationship to CD19 CART therapy
- Positive RCL test result
- Vector insertion site sequencing result with a mono-or oligoclonality pattern or in a location near a known human oncogene
- New malignancy (T-cell & non T-cell), other than the primary malignancy
- Progressive multifocal leucoencephalopathy (PML)
- Hepatitis B reactivation

In addition, at the specific request of a National Health Authority, the following SAEs will be reported in an expedited manner:

- Any SAE related to a study procedure
- All occurrences of CRS grade ≥ 3 (to be reported to National Health Authority on a monthly basis)
- All deaths regardless of attribution following lymphodepleting chemotherapy and/or CTL019 infusion and within 30 days of receiving CTL019 infusion
- Deaths attributed to CTL019 occurring 30 days post CTL019 infusion

Any SAEs experienced after the Month 60 (EOT) visit should only be reported to Novartis Drug Safety and Epidemiology (DS&E) if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

[redacted]

If the SAE is not previously documented in the [Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis DS&E department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable.

8.4 Pregnancies

No data are currently available to determine the duration of contraception after receiving CTL019. CTL019 is within Pregnancy Category C. Animal reproduction studies have not been conducted with CTL019. It is also not known whether CTL019 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Women regardless of age that may have child-bearing potential (defined as all women physiologically capable of becoming pregnant) are recommended to continue contraception until CAR cells are no longer present in blood as measured by PCR and for a minimum of 12 months from CTL019 infusion. Women who are not yet of reproductive potential are also to agree to use acceptable forms of contraception when they reach reproductive potential. Male participants must use highly effective methods of contraception for a period of 1 year after CTL019 infusion. Highly effective contraception methods include:

a. Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are NOT acceptable methods of contraception
b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
c. Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
d. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1 %), for example hormone vaginal ring or transdermal hormone contraception.
e. Use of intrauterine devices are excluded due to increased risks of infection and bleeding. However, IUD inserted prior to consent may remain in place, and a second method of contraception is mandated.
f. In case of use of oral contraception, women must be stable on the same pill for a minimum of 3 months before taking study treatment.

[redacted]

Women who are not of reproductive potential (defined as either <11 years of age, Tanner Stage 1, post-menopausal for at least 24 consecutive months or have undergone hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy) are eligible without requiring the use of contraception. Women who are not yet of reproductive potential are to agree to use acceptable forms of contraception when they reach reproductive potential if within 1 year of CTL019 or if CAR cells are present in the blood by PCR. Acceptable documentation includes written or oral documentation communicated by clinician or clinician's staff of one of the following:

a. Demographics show age <11
b. Physical examination indicates Tanner Stage 1
c. Physician report/letter
d. Operative report or other source documentation in the patient record
e. Discharge summary
f. Follicle stimulating hormone measurement elevated into the menopausal range

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy follow up in this study will end after birth or after any adverse pregnancy outcome associated with the end of the pregnancy. In the case of live birth the newborn will be followed up until 6 months of age to detect any developmental issue or abnormality that would not be seen at birth. Pregnancy outcomes must also be collected for the female partners of any males who received CTL019 in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to Novartis. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the CTL019 transduced cells to any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between Investigator Brochure (IB) updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent/assent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established prior to the enrollment of the first patient. The DMC will be responsible for reviewing at regular intervals the safety data of the patients treated in the study. The DMC will consist of members who are not involved in

[redacted]

patient recruitment or trial conduct, with at least two oncologists (at least one pediatric hematology/oncologist) and one biostatistician.

There will be an initial meeting with the DMC to have agreement on their roles and responsibilities and the potential data format and procedures that will be reviewed during the course of the study. The first DMC safety review meeting will be held when approximately the first 5 patients have been treated for at least 1 month or at least 6 months after the first patient is enrolled, whichever occurs first. Subsequent safety reviews will occur every six months, unless otherwise requested by the Chairman of the DMC. Additional meetings will be held by DMC or sponsor's requests at the time of some safety issues occurrence, especially when serious events (e.g., death) occur on the study or safety notifications regarding the study treatment outcome.

Detailed recruitment status and interim safety reports will be provided to the DMC on a regular basis.

Further details regarding the constitution of the DMC and its specific roles will be provided in the DMC charter prior to the enrollment of the first patient.

8.7 Steering Committee

The steering committee (SC) will be established comprising investigators participating in the trial, Novartis representatives from the Clinical Trial team and not members of the DMC. The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

8.8 Independent Review Committee (IRC)

An IRC will be established to review data related to disease response assessments during the Treatment and Primary Follow-up Phase and determine remission and relapse for the primary analysis. An IRC charter will detail the IRC data flow and review process in alignment with the response definitions in Appendix 1. Patient management will be based upon local investigator assessments. The designation of remission and relapse for the primary analysis and other related secondary efficacy endpoints will be based only on the evaluations made by the IRC. Details regarding the constitution of the IRC and its specific roles will be documented in the IRC charter agreed upon between Novartis and the IRC before initiation of any IRC reviews.

9 Data collection and management

9.1 Data confidentiality

Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization informing the patient of the following:

[redacted]

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research patient to revoke their authorization for use of their PHI

In the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the patient experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (patient initials and exact date of birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit patient initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the patient satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated Contract Research Organization [CRO]) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent/assent form (a copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent/assent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

[redacted]

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRFs are complete, accurate, and that entry and updates are performed in a timely manner.

The Novartis designated manufacturing facility is responsible for assuring that the manufacturing specific data entered into eCRFs are complete, accurate, and that entry and updates are performed in a timely manner.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history and adverse events will be coded using the MedDRA terminology.

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

The Novartis designated manufacturing facility is responsible for assuring that the manufacturing specific data entered into eCRFs are complete, accurate, and that entry and updates are performed in a timely manner.

10 Statistical methods and data analysis

Data from all participating centers will be combined.

An interim analysis will be performed when the first 50 patients who receive CTL019 have completed 3 months follow-up from study day 1 infusion or discontinued earlier. At the time of this interim analysis, assessment of all endpoints will be based only on patients who receive CTL019 manufactured from US manufacturing facility because there will be no patients treated with CTL019 manufactured from other manufacturing facilities.

The final analysis of the primary endpoint will be performed after all patients infused with CTL019 have completed 3 months follow-up from study day 1 infusion or discontinued earlier. Selected efficacy and safety analysis will be updated annually.

[redacted]

A final Clinical Study Report (CSR) will be produced once all patients complete the study.

10.1 Analysis sets

The analysis sets to be used are defined as below. The FAS will be used as the primary efficacy analysis set. The Safety Set will be used for all the safety analysis. The Pharmacokinetic Analysis Set (PAS) will be used for the pharmacokinetics analysis.

All tables and listings will be presented by one treatment arm of CTL019.

10.1.1 Screened Set

The Screened Set comprises all patients who have signed informed consent/assent and screened in the study.

10.1.2 Enrolled Set

The Enrolled Set comprises all patients who are enrolled in the study. Enrollment is defined as the point at which the patient meets all inclusion/exclusion criteria, and the patients' leukapheresis product is received and accepted by the manufacturing facility.

10.1.3 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned, and have received infusion of CTL019.

10.1.4 Interim Efficacy Analysis Set

At the time of interim analysis, the Interim Efficacy Analysis Set (IEAS) comprises the first 50 patients who receive CTL019 infusion.

10.1.5 Safety Set

The Safety Set comprises all patients who received infusion of CTL019.

10.1.6 Per-Protocol Set

The Per-Protocol Set (PPS) consists of a subset of the patients in the IEAS or FAS (at interim and final analysis respectively) who are compliant with major requirements of the clinical study protocol (CSP).

Major protocol deviations leading to exclusion from the PPS include:

- No diagnosis of ALL at baseline;
- Prior therapy does not match with CSP requirements in terms of number and types of previous therapy regimens;
- Missing or incomplete documentation of disease;

In addition, patients who receive a dose less than the minimum target dose of 2×10^6/kg (for patients $\leq$ 50 kg) or 1×10^8 (for patients > 50 kg) CTL019 transduced viable T cells will also be excluded.

The detailed exclusion criteria of PPS will be determined prior to primary analysis.

[redacted]

10.1.7 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of IEAS or FAS (at time of interim or final analysis respectively) who have at least one sample providing evaluable pharmacokinetic (PK) data. The PAS will be used for summaries (tables and figures) and listings of PK data.

Note that patients will be removed from the estimation of certain PK parameters on an individual basis depending on the number of available samples. These patients will be identified at the time of the analyses.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data will be listed by patient and/or summarized descriptively for the FAS as well as for IEAS. Categorical data will be presented as frequencies and percentages. For continuous data, summary statistics will be presented (i.e., mean, median, standard deviation, minimum, maximum).

Number and percentage of patients failing prior anti-neoplastic medications/therapies will be summarized.

Patients will be classified by the prior allogeneic SCT status (with prior SCT, without prior SCT).

Patients will also be classified by their prior response status into:

- Primary refractory: If patient never had a morphologic complete remission (CR) prior to the study
- Chemorefractory: If patient had no CR to further lines of therapy after relapse from 1st line therapy
- Relapsed disease: If patient had a CR from other therapy and relapsed prior to the study, and does not qualify for chemorefractory

10.3 Treatments (study treatment, concomitant therapies, compliance)

The total cells infused (cells/kg) and total CTL019 transduced viable T cells infused (cells/kg) will be listed and summarized using descriptive statistics. Patients will be categorized as below, within or above the prescribed dose range.

Prior and concomitant medications and significant non-drug therapies prior to and after the start of infusion will be listed by patient and summarized by the Anatomical Therapeutic Chemical (ATC) term. Transfusion during the study will be listed. In addition, whether patients have received anti-cytokine medications for the management of CRS will be summarized.

10.4 Primary objective

The primary objective of the study is to evaluate the efficacy of CTL019 therapy as measured by overall remission rate (ORR) rate during the 3 months after CTL019 administration, which includes CR and CR with incomplete blood count recovery (CRi) as determined by IRC assessment in the FAS population.

[redacted]

In addition, sensitivity analysis will be performed using the local investigator response assessments instead of the IRC assessment.

10.4.1 Variable

The primary endpoint is the ORR as determined by IRC assessment during the 3 months after CTL019 administration. The ORR is defined as the proportion of patients with a best overall disease response of CR or CRi, where the best overall disease response is defined as the best disease response recorded from CTL019 infusion until the start of new anticancer therapy. Best response will be assigned according to the following order:

- CR
- CRi
- No response (NR)
- Unknown

Table 10-1 Definition of CR, CRi and relapse at a given evaluation time

Response category	Definition
Complete remission (CR)	All the following criteria are met: **Bone marrow** • < 5% blasts **Peripheral blood** • Neutrophils > 1.0 x 10^9/L, and • Platelets > 100 x 10^9/L, and • Circulating blasts < 1% **Extramedullary disease** • No evidence of extramedullary disease (by physical exam and CNS symptom assessment) **Transfusion independency** • No platelet and/or neutrophil transfusions ≤ 7 days before peripheral blood sample for disease assessment
Complete remission with incomplete blood count recovery (CRi)	All criteria for CR as defined above are met, except that the following exist: • Neutrophils ≤ 1.0 x 10^9/L, and/or • Platelets ≤ 100 x 10^9/L, and/or • Platelet and/or neutrophil transfusions ≤ 7 days before peripheral blood sample for disease assessment
Relapsed Disease	Only in patients who obtained a CR or CRi: • Reappearance of blasts in the blood (≥ 1%), or • Reappearance of blasts in bone marrow (≥ 5%), or • (Re-)appearance of any extramedullary disease after CR or CRi

A full response evaluation, including assessments of peripheral blood, bone marrow, CNS symptoms, physical exam, and CSF assessment by LP, is required at the first time a CR or CRi is demonstrated. Bone marrow biopsy/aspirate and CSF assessment by LP are required 1 month (Day 28) after infusion. If the patient is not in CR/CRi at Month 1, then a bone marrow biopsy/aspirate and CSF assessment by LP are also required at the first time clinical evidence of remission is seen by peripheral blood and extramedullary disease assessment (physical

exam and CNS symptom assessment) to establish that a patient has achieved CR/CRi for the first time. Additional bone marrow biopsies/aspirates and CSF assessments by LP are not required after initial establishment of CR or CRi unless clinically indicated (recommended but not required at months 3 and 6).

Complete remissions in patients with ALL have been observed to take place within 1 month after infusion with CTL019. The onset of complete remissions are rapid and dramatic, and patients quickly regain a normal performance status. ALL relapse in the bone marrow is rapidly followed by signs or symptoms of disease recurrence as well as abnormalities in the peripheral blood.

Therefore, following initial achievement of CR/CRi, patients will be considered to have maintained a clinical CR/CRi if the patient has no evidence of extramedullary disease (by physical exam and CNS symptom assessment) and circulating blasts in peripheral blood are <1%. In order for the best ORR to be categorized as CR or CRi, there must be no clinical evidence of relapse as assessed by peripheral blood and extramedullary disease assessment (physical exam and CNS symptom assessment) at a minimum of 4 weeks (28 days) after the initial achievement of CR or CRi. Please note, if additional assessments of bone marrow and/or CSF are performed in the same evaluation, they will also need to show remission status.

See Appendix 1 for details of disease response criteria.

10.4.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis will be performed by testing whether the ORR within 3 months is less than or equal to 20% against the alternative hypothesis that ORR within 3 months is greater than 20% at overall one-sided 2.5% level of significance, i.e.,

$$H_0: p \leq 0.2 \text{ vs. } H_a: p > 0.2.$$

The primary efficacy endpoint, ORR within 3 months, will be analyzed at the interim look and final look of a group sequential design. The ORR will be summarized along with the 2-sided exact Clopper-Pearson confidence intervals with coverage level determined by the O'Brien-Fleming type α-spending approach according to Lan-DeMets as implemented in East 5.4 (Lan and DeMets, 1983). The study will be considered successful if the lower bound of the 2-sided exact confidence interval for ORR is greater than 20%, so that the null hypothesis that the ORR is less than or equal to 20% can be rejected.

The primary efficacy endpoint, ORR will be analyzed based on the data observed in the IEAS and FAS at interim and final analysis, respectively.

10.4.3 Handling of missing values/censoring/discontinuations

Patients in the study who are of unknown clinical response will be treated as non-responders. See also the Novartis guideline for efficacy evaluation in ALL (Appendix 1) for more details.

Other missing data are simply noted as missing on appropriate tables/listings.

10.4.4 Supportive analyses

The analysis of the primary endpoint will be performed among all patients in the PPS using the same methodology as outlined at interim and final analysis, respectively.

[redacted]

The analysis of primary endpoint will also be performed among all patients in the Enrolled Set who have either discontinued prior to CTL019 infusion or have received CTL019 infusion.

In addition, the analysis of the primary endpoint will also be performed using all patients who satisfy all clinical eligibility criteria and have either discontinued prior to CTL019 infusion or have received CTL019 infusion.

10.4.4.1 Subgroup analysis

Subgroup analyses will be performed on the following based on the patient's baseline status:

- Age: <10 years, ≥10 years to <18 years, ≥18 years
- Gender: Male, Female
- Race: White, Asian, Other
- Ethnicity: Hispanic or Latino, Other
- Prior response status: Primary refractory, Chemorefractory, Relapsed disease
- Prior SCT therapy: Yes, No
- Eligibility for SCT: Eligible for SCT, ineligible for SCT
- Baseline bone marrow tumor burden: Low (defined as either morphologic or MRD result is <50% and neither is ≥50%), High (defined as either morphologic or MRD result is ≥50%)
- Baseline extramedullary disease presence: Yes, No
- Philadelphia chromosome/BCR-ABL: Positive, Negative
- Mixed-Lineage Leukemia (MLL) rearrangement: Yes, No
- Hypoploidy: Yes, No
- *BCR-ABL1-like*: Yes, No
- Complex Karyotypes (≥5 unrelated abnormalities): Yes, No
- Down syndrome: Yes, No

The rationale for performing subgroup analyses are as follows:

- Age, gender, race and ethnicity are demographic factors that are typically requested by health authorities to assess internal consistency of the study results.
- Prior response status is a key prognosis factor due to potentially higher rates of treatment related morbidity in patients who have relapsed following allogeneic SCT.
- Baseline bone marrow tumor burden and extramedullary disease presence are important indicators of overall disease burden, which is a potential predictive factor.
- BCR-ABL, MLL rearrangement, hypoploidy, *BCR-ABL1-like* gene signatures and complex karyotype (≥ 5 unrelated abnormalities) are high risk factors for ALL. Patients with these high risk factors have poorer diagnosis (Harrison 2010; van der Veer 2013). In case there are very few patients with these high risk mutations individually, analysis may be performed for patients with any of these high risk mutations versus those who do not.
- Patients with Down Syndrome is known to have increased ALL treatment related morbidity and mortality rates. Because of increased risk, stem cell transplant is often not

[redacted]

recommended in this population. Therefore, the experience with CTL019 in this rare population may offer an unmet medical need.

Subgroup analyses will only be performed if at least 5 patients are present in each subgroup. Some grouping of classes will be considered if there are too few patients in some subgroups.

10.5 Secondary objectives

IRC assessment will be used in the main analysis of secondary endpoints that involve disease response.

10.5.1 Key secondary objective(s)

10.5.1.1 ORR within 3 months in all patients infused with CTL019 from US manufacturing facility

The first key secondary objective of the study is to evaluate the efficacy of CTL019 therapy from US manufacturing facilities as measured by overall remission rate (ORR) during the 3 months after CTL019 administration by IRC assessment.

The hypothesis testing will be performed to test whether the ORR within 3 months is less than or equal to 20% against the alternative hypothesis that ORR is greater than 20%.

This hypothesis testing will only be performed when the primary objective is met, so that the family-wise type I error rate will be controlled at one-sided 2.5% level under this hierarchical testing scheme. The type I error probability will be controlled by using a Lan-DeMets (O'Brien-Fleming) alpha spending function at 2.5% level of significance.

This key secondary endpoint will be summarized along with the 2-sided exact Clopper-Pearson confidence intervals with coverage level according to the above alpha spending function. This key secondary objective will be considered successfully met if the lower bound of the 2-sided exact confidence interval is greater than 20%, so that the null hypothesis above can be rejected.

10.5.1.2 Remission with MRD negative bone marrow in patients infused with CTL019 from all manufacturing facilities

The second key secondary objective of the study is to evaluate the percentage of patients who receive CTL019 from all manufacturing facilities and achieve a BOR of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry during the 3 months after CTL019 administration. The main analysis of this key secondary objective will be performed among all patients in the IEAS or FAS population, at the time of interim and final analysis respectively. See Appendix 1 for details of determination of MRD negativity.

This key secondary efficacy analysis will be performed by testing whether the percentage of MRD negative responder among all patients who received CTL019 infusion from all manufacturing facilities in IEAS or FAS as defined above is less than or equal to 15% against the alternative hypothesis that it is greater than 15% at overall one-sided 2.5% level of significance, i.e.,

$$H_0: p \leq 0.15 \text{ vs. } H_a: p > 0.15.$$

[redacted]

This hypothesis testing will only be performed when both the primary objective and the first key secondary endpoint are met, so that the family-wise type I error rate will be controlled at one-sided 2.5% level under this hierarchical testing scheme. The type I error probability will be controlled by using a Lan-DeMets (O'Brien-Fleming) alpha spending function at 2.5 % level of significance.

This key secondary endpoint will be summarized along with the 2-sided exact Clopper-Pearson confidence intervals with coverage level according to the above alpha spending function. This key secondary objective will be considered successfully met if the lower bound of the 2-sided exact confidence interval is greater than 15%, so that the null hypothesis above can be rejected.

The key secondary endpoint will also be summarized among who achieve a BOR of CR or CRi during the 3 months after CTL019 administration.

Additional analysis will be done using the qPCR MRD analysis instead of flow cytometry (exploratory only).

10.5.1.3 Remission with MRD negative bone marrow in patients infused with CTL019 from US manufacturing facility

The third key secondary objective of the study is to evaluate the percentage of patients who achieve a BOR of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry during the 3 months after CTL019 administration among all patients who receive CTL019 from US manufacturing facility.

The hypothesis testing will be performed to test whether the above rate is less than or equal to 15% against the alternative hypothesis that it is greater than 15%.

This hypothesis testing will only be performed when both the primary objective and the first two secondary endpoints are met, so that the family-wise type I error rate will be controlled at one-sided 2.5% level under this hierarchical testing scheme. The type I error probability will be controlled by using a Lan-DeMets (O'Brien-Fleming) alpha spending function at 2.5% level of significance.

This key secondary endpoint will be summarized along with the 2-sided exact Clopper-Pearson confidence intervals with coverage level according to the above alpha spending function. This key secondary objective will be considered successfully met if the lower bound of the 2-sided exact confidence interval is greater than 15%, so that the null hypothesis above can be rejected.

10.5.2 Other secondary efficacy objectives

The secondary efficacy objectives are outlined as follows in the order of importance.

Additional analyses will be performed to further assess the efficacy of CTL019 treatment by combining data collected in this protocol together with the 15 year long term follow-up protocol, if appropriate.

[redacted]

10.5.2.1 Percentage of patients who achieve CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment

The percentage of patients who achieve CR or CRi at Month 6 without SCT (post CTL019 infusion) between CTL019 infusion and Month 6 response assessment, among all patients in the FAS, will be summarized along with exact 95% Confidence Interval (CI). In addition, the percentage among patients who achieved CR or CRi will also be summarized. The time of proceeding to SCT is defined as the time of commencing the conditioning regimen as required for hematopoietic SCT. This definition applies to all analyses.

This analysis will be conducted when all patients have completed 6 months post CTL019 infusion or have discontinued earlier.

10.5.2.2 Percentage of patients who achieve CR or CRi and then proceed to SCT while in remission before Month 6 response assessment

The percentage of patients who achieve CR or CRi and then proceed to SCT while in remission by the time of Month 6, among all patients in the FAS, will be summarized along with exact 95% CI. In addition, the percentage will also be summarized among all patients who achieved CR or CRi.

This analysis will be conducted when all patients have completed 6 months post CTL019 infusion or have discontinued earlier.

All patients that proceed to SCT post CTL019 infusion will be listed.

10.5.2.3 Duration of remission (DOR)

Duration of remission (DOR) is defined as the duration from the date when the response criteria of CR or CRi is first met to the date of relapse or death due to underlying cancer.

In case a patient does not have relapse or death due to ALL prior to data cutoff, DOR will be censored at the date of the last adequate assessment on or prior to the earliest censoring event. The censoring reason could be:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy (also see below for handling SCT)
- Event after at least two missing scheduled disease assessments

In addition, death due to reason other than ALL will be considered as a competing risk event to other events of interest (relapse or death due to ALL).

As SCT is an important treatment option in responding patients, it is appropriate to consider the date of SCT as censoring date, instead of censoring at the last tumor assessment date. However, censoring due to SCT will overestimate the rate of relapse and therefore may be considered inappropriate for the main analysis when a substantial number of patients choose to receive SCT (CHMP 2010). If a patient received SCT after a CR or CRi, relapse or survival status after SCT will be recorded on the corresponding follow-up eCRFs, although data on individual disease response components (e.g. bone marrow) will not be collected. In such

[redacted]

cases, the date of relapse or death (if due to the underlying cancer) after SCT will be used for the calculation of DOR as a sensitivity analysis.

Additional sensitivity analysis will be performed by censoring death due to reason other than ALL instead of considering it as the competing risk event to other events of interest (relapse or death due to ALL).

The proposed analyses for DOR are summarized in Table 10-2 below. Method 1 will be considered as the main analysis for DOR. Additional analyses may be considered.

Table 10-2 Analyses of duration of response (DOR)

	Death due to reason other than ALL	SCT after remission
Method 1	Competing risk analysis	Censor at time of SCT
Method 2	Censor at last adequate tumor assessment	Censor at time of SCT
Method 3	Competing risk analysis	Ignore SCT
Method 4	Censor at last adequate tumor assessment	Ignore SCT

DOR will be assessed only in patients with the best overall response of CR or CRi. The estimated percentage of relapsed patients (at 6 months, 12 months, etc.) will be presented with 95% confidence intervals using the cumulative incidence function (CIF) or the Kaplan-Meier (KM) method.

For Method 1 and Method 3, the CIF is used to estimate the probability of the event of interest in the presence of the competing risks (Kim 2007).

For Method 2 and Method 4, the distribution function of DOR will be estimated using the KM method. The median DOR along with 95% confidence intervals will be presented if appropriate.

Method 1 and Method 3 will be conducted only if there are any patients who respond to CTL019 but experience the event of death due to reasons other than ALL.

If a considerable number of patients receive SCT while in remission after CTL019 infusion, then exploratory analyses may be performed on patients who achieve CR/CRi after CTL019 infusion to assess the effect of SCT on DOR. Baseline disease characteristics and post-baseline factors (e.g. time to CR/CRi, minimal residual disease) that may be correlated with the decision to receive SCT and with DOR will be identified. A Cox model with SCT as a time dependent covariate and potential confounding factors as additional covariates may then be explored in patients who achieve CR/CRi after CTL019 infusion. The hazard ratio (SCT v/s No SCT after CR/CRi) estimate along with its 95% confidence interval will be provided. Additional exploratory analyses may be considered to account for the confounding factors.

10.5.2.4 Relapse free survival (RFS)

Relapse free survival (RFS) is measured by the time from achievement of CR or CRi whatever occurs first to relapse or death due to any cause during CR or CRi.

In case a patient does not have relapse or death due to any cause prior to data cutoff, RFS will be censored at the date of the last adequate assessment on or prior to the earliest censoring event. The censoring reason could be

- Ongoing without event

[redacted]

- Lost to follow-up
- Withdrew consent
- New anticancer therapy (also see below for handling SCT)
- Event after at least two missing scheduled disease assessment

In the main analysis of RFS, patients who proceed to SCT after CTL019 infusion will be censored at the time of SCT. In addition, a sensitivity analysis of RFS will be performed without censoring SCT.

RFS will be assessed only in patients with the best overall response of CR or CRi. The distribution function of RFS will be estimated using the KM method. The median RFS along with 95% confidence intervals will be presented if appropriate.

10.5.2.5 Event free survival (EFS)

Event free survival (EFS) is the time from date of first CTL019 infusion to the earliest of the following:

- Death from any cause after remission
- Relapse
- Treatment failure: Defined as no response in the study and discontinuation from the study due to any of the following reasons:
  - Death
  - Adverse event (including abnormal laboratory values or abnormal test procedure results)
  - Lack of efficacy or progressive disease
  - New anticancer therapy

In case of treatment failure, the event date will be set to study Day 1 (CHMP 2010).

In case a patient does not have relapse, death due to any cause or treatment failure (e.g. discontinuation as a result of withdrawal of consent, lost to follow-up, protocol violation or administrative problems) prior to data cutoff, EFS is censored at the last adequate response assessment date on or prior to the earliest censoring event (except for SCT). The censoring reason could be

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy (also see below for handling SCT)
- Event after at least two missing scheduled disease assessment

In the main analysis of EFS, patients who proceed to SCT after CTL019 infusion will be censored at the time of SCT. In addition, a sensitivity analysis of EFS will be performed without censoring SCT.

[redacted]

EFS will be assessed in all patients in IEAS and FAS. The distribution function of EFS will be estimated using the KM method. The median EFS along with 95% confidence intervals will be presented if appropriate.

10.5.2.6 Overall survival (OS)

Overall survival (OS) is the time from date of first CTL019 infusion to the date of death due to any reason.

In case a patient is alive at the date of last contact on or before data cutoff, OS is censored at the date of last contact. No censoring will be done in case of SCT. Thus, patients should be followed-up for survival also in case of SCT.

OS will be assessed in all patients in IEAS and FAS. The distribution function of OS will be estimated using the Kaplan Meier (KM) method. The median OS along with 95% confidence intervals will be presented if appropriate.

10.5.2.7 Patient Reported Outcome

Patient Reported Outcome (PRO), such as scores of health-related quality of life questionnaires PedsQL and EQ-5D will be assessed. PedsQL™ will be completed by patients aged 8 and above, and EQ-5D will be completed by patients aged 8 and above. Descriptive statistics (e.g. mean, median, and frequency) and change from baseline of the summary scores for each post baseline time-point/window of assessment will be provided based on all available data at the time of final analysis. FAS will be used for all analysis.

10.5.2.8 Response at Day 28 +/- 4 days

Proportion of patients attaining CR or CRi at Day 28 +/- 4 days post CTL019 infusion, in the same analysis set as for the primary endpoint, will be summarized along with exact 95 % Confidence Interval (CI).

10.5.2.9 Impact of baseline tumor burden on response

Best overall response will be summarized by baseline tumor burden (MRD, extramedullary disease, etc).

10.5.2.10 Quality of response using MRD disease assessments

The quality of response using MRD disease assessments before treatment, and at day 28 +/- 4 days after treatment using central assessment by flow cytometry and before SCT by local assessment (flow or PCR) will be summarized descriptively.

Both quantitative MRD result and qualitative results (positive/negative) will be summarized if available.

10.5.2.11 Efficacy, safety and CTL019 PK in patients infused with CTL019 manufactured by [redacted]

The ORR and MRD negative remission rate will be summarized with 95% exact confidence intervals for patients infused with CTL019 manufactured by [redacted].

[redacted]

Key safety summaries for adverse events regardless of relationship to study drug by System Organ Class (SOC) and PT, and adverse events of special interest will be performed on the Safety Set.

The CTL019 PK parameters for CTL019 transgene levels as measured by q-PCR will also be summarized. The CTL019 PK parameters as measured by flow cytometry (exploratory only) will also be summarized, as appropriate.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by one treatment arm of CTL019.

The overall observation period will be divided into two mutually exclusive segments:

- pre-infusion period: from day of patient's informed consent/assent to the day before infusion of CTL019
- post-infusion period: starting at day of CTL019 infusion

10.5.3.2 Adverse events (AEs)

Reporting of adverse events will be based on MedDRA and CTCAE version 4.03.

Summary tables for adverse events have to include only AEs that started or worsened during the post-infusion period, i.e. the **treatment-emergent** AEs. However, all safety data (including those from the pre-infusion period) will be listed and those collected during the pre-infusion period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class, preferred term, severity (based on CTCAE grades), and relation to study treatment. A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event. The frequency of Common Toxicity Criteria (CTC) grade 3 and 4 AEs will be summarized separately.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.

Adverse events of special interest (AESI) search criteria are updated on a regular basis at the CTL019 program level. The most recent version of the AESI search criteria form will be used for the reporting activity. The current AESI search criteria are described in Table 10-3 below. AESI that occur within 8 weeks of the CTL019 infusion will be summarized by group term and preferred term.

[redacted]

Table 10-3 Adverse events of special interest (AESI) search criteria

AESI group term	MedDRA term or other search criteria	Type
Cytokine Release Syndrome	Cytokine Release Syndrome	PT
	Cytokine storm	PT
	Shock	PT
	Macrophage Activation	PT
	Histiocytosis haematophagic	PT
Tumor Lysis Syndrome	Tumor Lysis Syndrome	SMQ
Febrile neutropenia	Neutropenic infection	PT
	Neutropenic sepsis	PT
	Febrile neutropenia	PT
Infection	Infections and infestations	SOC
Transient neuropsychiatric events	Noninfectious encephalopathy/ delirium	SMQ
Hematopoietic cytopenias not resolved by day 28	Haematopoietic cytopenias	SMQ
	Lab abnormalities which do not resolve at least 28 days post CTL019 infusion	Lab

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by the CTCAE, the study's biostatistics and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- shift tables using CTCAE grades to compare baseline to the worst post-infusion value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time-course of raw or change in laboratory tests over time or box plots might be specified in the Master Analysis Plan (MAP) and/or the Report and Analysis Plan (RAP).

10.5.3.4 Immunogenicity

Humoral immunogenicity assessment will include evaluation of pre-existing (pre-treatment) and post-treatment anti-CTL019 antibodies and to examine the incidence of immunogenicity with treatment, together with antibody titers, as a secondary endpoint. Data may be further fractionated to determine proportion of patients who make transient versus sustained antibody responses. The assay for humoral immunogenicity will be a cell-based assay, detecting antibodies that bind to a Jurkat cell line transfected with the CTL019 construct. This cell line stably expresses the complete CTL019 sequence and can be used to detect antibodies that bind to any epitope on the extracellular domain of the protein. Cellular immunogenicity assessment will include percentage of CD4+ and CD8+ T cells specific for CTL019 as an exploratory analysis and reported as appropriate.

[redacted]

10.5.3.5 Derivation of a score to predict cytokine release syndrome

Clinical and biomarker data will be analyzed to potentially identify an early predictive score which reflects the risk of developing severe cytokine release syndrome. Only parameters that can be potentially utilized in clinical setting by treating physicians will be considered for the score development.

10.5.3.6 Soluble immune factors

Soluble immune and inflammatory cytokines (e.g. IL-10, interferon gamma, IL-6, IL-6 receptor, CRP, and ferritin) will be listed and summarized by patient and time point. Baseline and absolute and relative change (percent and or fold change) from baseline will be calculated for each treatment group and time point and summarized using sample size, mean, standard deviation, median, minimum and maximum. If both the baseline and post baseline values are below LLOQ, absolute, percent and fold change from baseline will not be imputed and reported as missing. Baseline levels may also be summarized by clinical response status and severity of CRS and potentially graphed using strip plots. In addition, the maximum change from baseline measure for each cytokine may also be graphed against clinical response status and severity of CRS response using strip plots. Patient level and averaged cytokine measures and percent change from baseline may be displayed using longitudinal plots.

The general principles of analyzing biomarker data as outlined in Section 10.6.1 should also apply.

10.5.3.7 B-cell and T-cell level

The levels of B and T cells (peripheral blood and bone marrow) prior to and following CTL019 infusion will be described.

Malignant and normal B cell populations will be listed and summarized by patient and time point. Baseline and absolute and relative change (percent change) from baseline will be calculated and summarized using sample size, mean, standard deviation, median, minimum and maximum. Baseline and change from baseline to minimum cell number may also be summarized by response status and potentially graphed using strip plots. Patient level and averaged cell counts and percent change from baseline may be displayed using longitudinal plots.

It is anticipated that all patients who achieve complete remission will exhibit B-cell aplasia. Timing of B-cell recovery will be summarized.

CD8 and CD4 positive T cells will be listed and summarized by time point. Data may also be summarized by response status and potentially graphed using strip plots. Patient level and average longitudinal plots of the cell counts and percent changes from baseline may be generated.

The general principles of analyzing biomarker data as outlined in Section 10.6.1 should also apply.

For abnormal T cell or B cell results, associated safety events such as infections and use of associated therapies (i.e. antibiotics, immunoglobulin replacement) will be investigated using patient listings

[redacted]

10.5.3.8 Other safety data

Vital signs will be collected as clinically needed. Findings supportive of GVHD will be listed for patients who have received prior allogeneic SCT. All safety data will be listed.

10.5.3.9 Safety subgroup analysis

Key safety summaries for adverse events regardless of relationship to study drug by System, Organ, Class (SOC) and PT, and adverse events of special interest will be repeated on the Safety Set in the following subgroups:

- Age: <10 years, ≥10 years to <18 years, ≥18 years
- Gender: Male, Female
- Race: White, Asian, Other
- Ethnicity: Hispanic or Latino, Other
- Prior response status: Primary refractory, Chemorefractory, Relapsed disease
- Prior SCT therapy: Yes, No
- Down syndrome: Yes, No

The objective of carrying out these subgroup analyses is to identify safety problems that are limited to a subgroup of patients or that are more commonly observed in a subgroup of patients.

Summary tables will only be performed if at least 5 patients are present in each subgroup. Some grouping of classes will be considered.

10.5.4 Pharmacokinetics

CTL019 concentrations in peripheral blood (and bone marrow and CSF if available) will be listed, graphed, and summarized by time point as assessed by the following (see Section 10.6.1):

- CTL019 transgene levels as measured by q-PCR,
- CTL019 transduced cells measured by flow cytometry of CD3-positive,
- CTL019 transduced cells measured by flow cytometry of CD3-positive/ CD4-positive and CD3-positive/CD8-positive CTL019 transduced cells. (exploratory only)

The PK parameters listed in Table 10-4 along with other relevant PK parameters will be estimated from the individual concentration versus time profiles using a non-compartmental approach within the modeling program Phoenix® (Pharsight, Mountain View, CA). The non-quantifiable concentrations will be imputed to zero for PK concentration summaries, and will not be included for estimation of PK parameters. Results reported but deemed unreliable will be flagged and excluded from the summaries and PK parameter derivations.

[redacted]

Table 10-4 Noncompartmental pharmacokinetic parameters

Parameter	Definition
AUC 0 - Tmax	The AUC from time zero to T_{max} in peripheral blood (% or copies/µg x days)
AUC Tmax - 28d and M3	The AUC from time Tmax to day 28 and M3 or other disease assessment days, in peripheral blood (% or copies/µg x days)
AUC 0 - 28d and M3	The AUC from time zero to day 28 and M3 or other disease assessment days, in peripheral blood (% or copies/µg x days)
Cmax	The maximum (peak) observed in peripheral blood or other body fluid drug concentration after single dose administration (% or copies/µg)
Tmax	The time to reach maximum (peak) peripheral blood or other body fluid drug concentration after single dose administration (days)
T1/2	The half-life associated with the elimination phase slope of a semi logarithmic concentration-time curve (days) in peripheral blood
Clast	The last observed quantifiable concentration in peripheral blood (% or copies/µg)
Tlast	The time of last observed quantifiable concentration in peripheral blood (days)

Descriptive statistics of PK parameters will be summarized by mean, standard deviation, coefficient of variation, min and max. When a geometric mean will be presented, it will be stated as such. A range of values will be presented for selected variables. Since T_{max} is generally evaluated by a nonparametric method, median values and ranges will be given for this parameter.

The relationship between anti-cytokine treatment, use of steroids, occurrence of immunogenicity or other relevant covariates and PK will be explored. Population or mechanistic PK/PD models may also be generated for ALL patients. For patients whose tocilizumab PK data were collected during CRS, the tocilizumab concentrations will be summarized by time points, relative to time of tocilizumab dose as appropriate and supported by data.

10.6 Exploratory objectives

10.6.1 Biomarkers

As a project standard, Novartis Oncology Biostatistics and Data Management will analyze only biomarkers collected in the clinical database. For exploratory markers, since the studies are not adequately powered to assess specific biomarker–related hypotheses, the goal of these exploratory statistical analyses should be considered as the generation of new scientific hypotheses or observing new trends. These hypotheses may be compared with results found in literature as well as verified with data derived from subsequent clinical trials. No adjustment for multiple comparisons is usually planned for exploratory analyses. Furthermore, additional post hoc exploratory assessments are expected and may be performed.

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue the analysis of blood due to either practical or strategic reasons (e.g. issues related to the quality of the sample). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

[redacted]

10.6.1.1 Biomarker Data Analysis Set

The Full Analysis Set will be used for all biomarker analysis. Unless otherwise specified, all statistical analyses of biomarker data will be performed on patients with biomarker data.

10.6.1.2 Data handling

Serum cytokine data are generally log normally distributed. A Log2 transformation of the data is typically required for normalization prior to performing any statistical assessments. Values below the lower limit of quantitation (which may be reported with the label Lower Limit of Quantification [LLOQ]) or have a numerical value below the assay's lower limit of quantification) will be imputed / replaced as 0.5×LLOQ, which will be specified by the performing lab and is assay and analyte specific. In some cases a value, although below LLOQ, is reported, this value should not be used and the data should be imputed as 0.5×LLOQ.

10.6.1.3 Basic tables, listings and figures

The ALL clonal distribution as measured by IgH deep sequencing will be listed per patient and percent change from baseline will be summarized using sample size, mean, standard deviation, median, minimum and maximum. Patient level absolute and relative changes may be displayed using longitudinal plots. Additional analyses [redacted] that may be performed after the completion of the end-of-study CSR will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in an addendum of the RAP or in a stand-alone analysis plan document, as appropriate.

10.6.2 CTL019 product characteristics

Selected clinical outcomes will be summarized descriptively by CTL019 product characteristics [redacted]

10.6.3 Cytokine release syndrome

To explore the relationship between CRS and other endpoints, the goal of this statistical analysis should be considered as the generation of new scientific hypotheses and observing new trends, since the studies are not adequately powered to propose a scoring system. Information regarding the severity of cytokine release syndrome, and response to anti-cytokine therapy, if any, will be listed and summarized. The summarization is descriptive only to be in line with its exploratory nature. Summary by initial tumor burden, clinical tumor response status, and PK/PD parameters may be explored.

10.6.4 Healthcare resource utilization

Data relating to resource utilization (described in Section 7.2.6) will be used to support health economic evaluations.

[redacted]

Number of CTL019 inpatients and outpatients infusions will be summarized. Descriptive statistics of hospitalizations, including the total and average number and duration of hospitalizations, will be provided.

Details of data analysis will be specified in the analysis plan as appropriate.

10.7 Interim analysis

10.7.1 Interim analysis for the primary endpoint

An interim analysis is planned when the first 50 patients infused have completed 3 months from study day 1 infusion or discontinued earlier. The interim analysis will be performed by testing the null hypothesis of ORR within 3 months being less than or equal to 20% against the alternative hypothesis of ORR within 3 months being greater than 20% at overall one-sided 2.5% level of significance.

The study will not be stopped for outstanding efficacy at the interim analysis regardless of the interim result.

An α-spending function according to Lan-DeMets (O'Brien-Fleming), as implemented in East 5.4, will be used to construct the efficacy stopping boundaries (Lan and DeMets 1983). Based on the choice of α-spending functions described above, if the interim analysis is performed exactly with 50 patients and final analysis will include up to 76 patients (i.e. 50/76=65.8% information fraction), the lower bound of the 2-sided 98.9% exact CI of the ORR will need to be greater than 20% to declare statistical significance. As a result, an ORR of 19/50 = 38% is needed to claim success at interim. If the interim efficacy boundary is not crossed, 2-sided 95.4% exact CI will be used at final analysis correspondingly. As a result, an ORR of 23/76 = 30% will be needed to claim success at final analysis.

The efficacy boundary at the final analysis will be based on the actual number of patients and the alpha already spent at the interim analysis. If the number of patients in the final analysis deviates from the expected number of patients, the final analysis criteria will be determined so that the overall significance level across all analyses is maintained at one-sided 0.025.

10.7.2 Interim analysis for the key secondary endpoints

If the primary endpoint is met at the interim analysis, the key secondary endpoints will also be assessed following hierarchical sequence using an α-spending function according to Lan-DeMets (O'Brien-Fleming).

10.7.2.1 ORR within 3 months in all patients infused with CTL019 from US manufacturing facility

Based on the choice of α-spending functions described above, if the interim analysis is performed exactly with 50 patients and final analysis will include up to 66 patients (i.e. 50/66=75.8% information fraction), the lower bound of the 2-sided 98.0% exact CI of the ORR will need to be greater than 20% to declare statistical significance. As a result, an ORR of 18/50 = 36% is needed to claim success at interim. If the interim efficacy boundary is not crossed, 2-sided 95.6% exact CI will be used at final analysis correspondingly. As a result, an ORR of 21/66 = 32% will be needed to claim success at final analysis.

[redacted]

10.7.2.2 Remission with MRD negative bone marrow in patients infused with CTL019 from all manufacturing facilities

Based on the choice of α-spending functions described above, if the interim analysis is performed exactly with 50 patients and final analysis will include up to 76 patients (i.e. 50/76=65.8% information fraction), the lower bound of the 2-sided 98.9% exact CI will need to be greater than 15% to declare statistical significance. As a result, a MRD negative rate of 15/50 = 30% is needed to claim success at interim. If the interim efficacy boundary is not crossed, 2-sided 95.4% exact CI will be used at final analysis correspondingly. As a result, an ORR of 19/76 = 25% will be needed to claim success at final analysis.

10.7.2.3 Remission with MRD negative bone marrow in patients infused with CTL019 from US manufacturing facility

Based on the choice of α-spending functions described above, if the interim analysis is performed exactly with 50 patients and final analysis will include up to 66 patients (i.e. 50/66=75.8% information fraction), the lower bound of the 2-sided 98.0% exact CI of the ORR will need to be greater than 20% to declare statistical significance. As a result, an ORR of 15/50 = 30% is needed to claim success at interim. If the interim efficacy boundary is not crossed, 2-sided 95.6% exact CI will be used at final analysis correspondingly. As a result, an ORR of 17/66 = 26% will be needed to claim success at final analysis.

10.8 Sample size calculation

In a previous study of clofarabine in patients with r/r B-cell ALL who have had 2 or more prior regimens, the reported ORR was 20% (95% CI [10%, 34%], Jeha et al (2006)). Hence, an ORR of 45% that excludes a 20% ORR at the 0.025 significance level would indicate meaningful efficacy in this highly refractory population.

The final analysis of the primary endpoint will be performed after all patients infused with CTL019 have completed 3 months follow-up from study day 1 infusion or discontinued earlier. The sample size for the final analysis of the primary endpoint will be up to 76 patients.

Based on the null hypothesis of ORR ≤ 20% and alternative hypothesis of ORR > 20%, 76 patients in the FAS will provide more than 95% power to demonstrate statistical significance at one-sided 0.025 level of significance, if the underlying ORR is 45%, taking into account the interim analysis as described in Section 10.7. In this setting, an ORR of 30% (=23/76) will be needed to claim success.

Within the expected sample size of 76 patients with CTL019, at least 10 patients will be treated with CTL019 manufactured by the [redacted]. If there are at least 6 patients among them who achieved best overall response of CR or CRi, the lower bound of the 95% confidence interval will be higher than 20%. The probability of observing at least 6 CR or CRi among the 10 patients will be 26% if the true ORR is 45%, and will be 84% if the true ORR is 70%.

Table 10-5 Confidence intervals for ORR in patients infused with CTL019 manufactured by the [redacted]

Total number of patients	CR + CRi	95% Exact CI
[redacted]		

10	5	(18.7%, 81.3%)
	6	(26.2%, 87.8%)
	7	(34.8%, 93.3%)
	8	(44.4%, 97.5%)
	9	(55.5%, 99.7%)
	10	(69.2%, 100%)

The actual number of patients to be enrolled will depend on the pre-infusion dropout rate. Limited data are available so far to provide robust estimate on the pre-infusion dropout rate. Assuming 20% to 25% enrolled patients will not be infused due to reasons such as CTL019 product manufacturing issues, worsening of patient's condition, etc., approximately 95 patients need to be enrolled respectively to reach the number of patients required.

10.9 Power for analysis of key secondary variables

10.9.1 ORR within 3 months in patients infused with CTL019 from US manufacturing facility

The same efficacy is assumed for patients infused with CTL019 in US manufacturing facility vs other manufacturing facilities. Under this assumption and conditional on the statistical significance of the primary endpoint, the over power of this endpoint will be greater than 95%, taking in account an interim analysis will be performed with first 50 patients, and then a final analysis will be performed with up to 66 patients with CTL019 from US manufacturing facility.

10.9.2 Remission with MRD negative bone marrow in patients who received CTL019 from all manufacturing facilities

In previous studies in the r/r ALL setting, 67% to 82% patients achieved MRD negative status among patients who achieved CR or CRi (Topp et al 2015, O'Brien et al 2012). Considering that an ORR of 45% that excludes 20% at the 0.025 significance level would indicate meaningful efficacy for ORR, 34% of patients achieving MRD negative bone marrow that excludes 15% at the 0.025 significance level would indicate meaningful efficacy (i.e. 75% among complete responders) for the key secondary objective.

Based on the above assumptions, conditional on the statistical significance of the primary and the first key secondary endpoint, and taking into account the interim analysis with first 50 patients as described above, up to 76 patients in the FAS will provide greater than 95 % power to demonstrate statistical significance at one-sided 0.025 level of significance, if the underlying percentage of patients who achieve BOR or CR or CRi with MRD negative bone marrow is 34%.

10.9.3 Remission with MRD negative bone marrow in patients who received CTL019 from US manufacturing facility

The same efficacy is assumed for patients infused with CTL019 in US manufacturing facility vs other manufacturing facilities. Under this assumption and conditional on the statistical significance of the primary and first 2 key secondary endpoints, the power of this endpoint will be 94%, taking in account an interim analysis will be performed with first 50 patients,

[redacted]

and then a final analysis will be performed with up to 66 patients with CTL019 from US manufacturing facility.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent/assent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent/assent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent/assent should be documented in the patient source documents. The date when a patient's informed consent/assent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) and assent form that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF/assent suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the

[redacted]

duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.3.

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study electronic case report form (eCRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. For eCRFs an audit trail will be maintained by the system.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by

[redacted]

applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless the sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis, with the exception of information required to manufacture CTL019 product provided to limited personnel at the manufacturing facility. Signed informed consent/assent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. United Kingdom (UK) requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

[redacted]

13 References (available upon request)

Aiuti A, Biasco L, Scaramuzza S, et al. (2013) Lentiviral hematopoietic stem cell gene therapy in patients with Wiskott-Aldrich syndrome. Science 341(6148):1233151

Anon (2010) CHMP (2010) Appendix 2 to the Guidance on the evaluation of anticancer medicinal products in man (CPMP/EWP/205/95 Rev. 3) on confirmatory studies in haematological malignancies. Available from <.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500074949.pdf>

Anon (2013) National cancer institute. Surveillance epidemiology and end results. Available from seer.cancer.gov/

Anon (2013) National Comprehensive Cancer Network (NCCN) Guidelines (NCCN, 2013 vl), Acute Lymphoblastic Leukemia. Available from nccn.org/professionals/physician_gls/f_guidelines.asp#site

Appelbaum FR (2001) Haematopoietic cell transplantation as immunotherapy. Nature; 411(6835):385-389

Appelbaum FR, Rosenblum D, Arceci RJ, et al. (2007) End points to establish the efficacy of new agents in the treatment of acute leukemia. Blood 109(5):1810-1816

Biffi A, Montini E, Lorioli L, et al. (2013) Lentiviral hematopoietic stem cell gene therapy benefits metachromatic leukodystrophy. Science 341(6148):1233158

Brentjens R, Yeh R, Bernal Y, et al. (2010) Treatment of chronic lymphocytic leukemia with genetically targeted autologous T cells: case report of an unforeseen adverse event in a phase I clinical trial. Mol Ther; 18(4):666-668

Brentjens RJ, Latouche J, Santos E, et al. (2003) Eradication of systemic B-cell tumors by genetically targeted human T lymphocytes co-stimulated by CD80 and interleukin-15. Nat. Med 9:279-286

Cairo MS, Bishop M (2004) Tumor lysis syndrome: new therapeutic strategies and classifications. Br J Haematol; 127 (1):3-11

Calogero A, DeLeij LFMH, Mulder N, et al. (2000) Recombinant T-cell receptors: an immunologic link to cancer therapy. J Immunol; 23(4):393-400

Cheson B, Bennet JM, Kopecky K, et al. (2003) Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol; 21(24):4642-9

Clay T, Morse M, Lyerly HK (2002) Redirecting cytotoxic T lymphocyte responses with T-cell receptor transgenes. Expert Opin Biol Ther; 2(4):353-360

Cooper L, Topp M, Serrano LM, et al. (2003) T-cell clones can be rendered specific for CD19: toward the selective augmentation of the graft-versus-B-lineage leukemia effect. Blood 101(4):1637-1644

Dudley ME, Wunderlich JR, Robbins P, et al. (2002) Cancer regression and autoimmunity in patients after clonal repopulation with antitumor lymphocytes. Science; 298:850-854

[redacted]

Dudley ME, Wunderlich JR, Yang JC, et al. (2005) Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol; 23(10):2346-2357

Dummer W, Niethammer AG, Baccala R, et al. (2002) T cell homeostatic proliferation elicits effective antitumor autoimmunity. J. Clin Invest; 110(2):185-192

Duval M, Klein JP, He W, et al. (2010) Hematopoietic Stem-Cell Transplantation for Acute Leukemia in Relapse or Primary Induction Failure. J Clin Oncol; 28:3730-8

Eshhar Z, Waks T, Bendavid A, et al. (2001) Functional expression of chimeric receptor genes in human T cells. J Immunol Methods; 248:67-76

European Medicines Agency (2008) Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products. Available from <.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500006326.pdf>

European Medicines Agency (2009) Guideline on Follow-up of Patients Administered with Gene Therapy Medicinal Products. Available from <.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/11/WC500013424.pdf>

Fearon D, Carroll M (2000) Regulation of B lymphocyte responses to foreign and self-antigens by the CD19/CD21 complex. Annu Rev Immunol; 18:393-422

Finney H, Akbar A, Lawson A (2004) Activation of resting human primary T cells with chimeric receptors: costimulation from CD28, inducible, costimulator, CD134 and CD137 in series with signals from the TCR zeta chain. J Immunol; 172(1):104-113

Finney H, Lawson A, Bebbington C, et al. (1998) Chimeric receptors providing both primary and costimulatory signaling in T cells from a single gene product. J Immunol; 161(6):2791-2797

Food and Drug Administration (2006a) Guidance for Industry: Gene therapy clinical trials-–Observing subjects for delayed adverse events. Available from <.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm072957.htm>

Food and Drug Administration (2006b) Guidance for Industry: Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors. Available from <.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm072961.htm>

Friedmann-Morvinski D, Bendavid A, Waks T, et al. (2005) Redirected primary T cells harboring a chimeric receptor require costimulation for their antigen-specific activation. Blood; 105(8):3087-3093

Goldrath AW, Bevan MJ (1999) Selecting and maintaining a diverse T-cell repertoire. Nature 402(6759):255-262

Gross G, Eshhar Z (1992) Endowing T cells with antibody specificity using chimeric T cell receptors. FASEB J; 6:3370-3378

[redacted]

Gross G, Waks T, Eshhar Z (1989) Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity. Proc Natl Acad Sci USA; 86(24):10024-10028

Grupp SA, Kalos M, Barrett D, et al. (2013) Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. N Engl J Med; 368(16):1509-1518

Harrison CJ, Haas O, Harbott J, et al. (2010) Detection of prognostically relevant genetic abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia: recommendations from the Biology and Diagnosis Committee of the International Berlin-Frankfürt-Münster study group. Brit J Hematol; 151(2):132-142

Hombach A, Heuser C, Abken H (2002) The recombinant T cell receptor strategy: insights into structure and function of recombinant immunoreceptors on the way towards an optimal receptor design for cellular immunotherapy. Curr Gene Ther; 2:211-226

Hoofnagle JH (2009) Reactivation of hepatitis B. Hepatology; 49(5 Suppl):S156-65

Jeha S, Gandhi V, Chan KW, et al. (2004) Clofarabine, a novel nucleoside analog, is active in pediatric patients with advanced leukemia. Blood, 103(3):784-789

Jeha S, Gaynon PS, Razzouk BI, et al. (2006) Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. J Clin Oncol, 24(12):1917–1923

June CH (2007) Adoptive T cell therapy for cancer in the clinic. J Clin Invest 117;1466-1476

June CH, Blazar BR, Riley JL (2009) Lymphocyte Subset Engineering: tools, trials and tribulations. Nat Rev Immunol 9(10):704-716

Kaech SM, Ahmed R (2001) Memory CD8+ T cell differentiation: initial antigen encounter triggers a developmental program in naive cells. Nat Immunol 2(5):415-422

Kim H (2007) Cumulative incidence in competing risks data and competing risks regression analysis. Clin Cancer Res; 13(2 Pt 1):559-565

King C, Ilic A, Koelsch K, et al. (2004) Homeostatic expansion of T cells during immune insufficiency generates autoimmunity. Cell; 117:265-277

Klebanoff CA, Khong HT, Antony PA, et al. (2005) Sinks, suppressors and antigen presenters: how lymphodepletion enhances T cell-mediated tumor immunotherapy. Trends Immunol; 26(2):111-117

Ko RH, Ji L, Barnette P, et al. (2010) Outcome of patients treated for relapsed or refractory acute lymphoblastic leukemia: therapeutic advances in childhood leukemia consortium study. J Clin Oncol; 28:648-654

Kohn DB, Dotti G, Brentjens R, et al. (2011) CARS on track in the clinic. Mol Ther; 19(3):432-438

Kolb HJ, Schattenberg A, Goldman JM, et al. (1995) Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. European group for blood and marrow transplantation working party chronic leukemia. Blood; 86(5):2041-2050

Krause A, Guo HF, LaTouche JB, et al. (1998) Antigen-dependent CD28 signaling selectively enhances survival and proliferation in genetically modified activated human primary T lymphocytes. J Exp Med; 188(4):619-626

[redacted]

Lamers CH, Sleijfer S, Vulto A, et al. (2006) Treatment of metastatic renal cell carcinoma with autologous T-lymphocytes genetically retargeted against carbonic anhydrase ix: first clinical experience. J Clin Oncol; 24(13):20e-22e

Laport GG, Levine BL, Stadtmauer EA, et al. (2003) Adoptive transfer of costimulated T cells induces lymphocytosis in patients with relapsed/refractory non-Hodgkin lymphoma following CD34+-selected hematopoietic cell transplantation. Blood; 102(6):2004-2013

Ledbetter J, Rabinovitch P, June C, et al. (1988) Antigen-independent regulation of cytoplasmic calcium in b cells with a 12-kDa b-cell growth factor and anti-CD19. Proc Natl Acad Sci USA; 85(6):1897-1901

Maher J, Brentjens R, Gunset G, et al. (2002) Human T-lymphocyte cytotoxicity and proliferation directed by a single chimeric TCR zeta/ CD28 receptor. Nat Biotechn; 20:70-75

Martin A, Morgan E, Hijiya N (2012) Relapsed or Refractory Pediatric Acute Lymphoblastic Leukemia: Current and Emerging Treatments. Pediatric Drugs; 14(6):377-87

Maude S, Frey N, Shaw P, et al. (2014) Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia. N Engl J Med; 371:1507-17

Mellman I, Coukos G, Dranoff G (2011) Cancer immunotherapy comes of age. Nature; 480(7378):22-29

Milone M, Fish J, Carpenito C, et al. (2009) Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy *in vivo*. Mol Ther Nucleic Acids; 17(8):1453-1464

Mitchell ME, Lowe K, Fryzek J (2012) A multisource approach to improving epidemiologic estimates: application to global B-cell malignancies. ISRN Oncol; 2012: 129713-129722

Mullaney BP, Pallavicini MG (2001) Protein-protein interactions in hematology and phage display. Exp Hematol; 29(10):1136-1146

O'Brien S, Schiller G, Lister J, et al. (2013) High-dose vincristine sulfate liposome injection for advanced, relapsed, and refractory adult Philadelphia chromosome-negative acute lymphoblastic leukemia. J Clin Oncol; 31(6):676-83

Oudot C, Auclerc MF, Levy V, et al. (2008) Prognostic factors for leukemic induction failure in children with acute lymphoblastic leukemia and outcome after salvage therapy: the FRALLE 93 study. J Clin Oncol; 26:1496-503

Palmer DC, Balasubramaniam S, Hanada K, et al. (2004) Vaccine-stimulated, adoptively transferred CD8+ T cells traffic indiscriminately and ubiquitously while mediating specific tumor destruction. J. Immunol; 173(12):7209-7216

Patel A, Yapali S, Lok A (2015) Admissions for hepatitis B reactivation in patients receiving immunosuppressive therapy remain unchanged from 1999 to 2014. Hepatol Int; 10(1):139-46

Pinthus JH, Waks T, Kaufman-Francis K, et al. (2003) Immuno-gene therapy of established prostate tumors using chimeric receptor-redirected human lymphocytes. Cancer Res; 63(10):2470-2476

Porter D, Levine B, Bunin N, et al. (2006) A phase 1 trial of donor lymphocyte infusions expanded and activated *ex vivo* via CD3/CD28 combination. Blood; 107(4):1325-1331

[redacted]

Porter D, Levine B, Kalos M, et al. (2011) Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. N Engl J Med; 365(8):725-733

Pule M, Finney H, Lawson A (2003) Artificial T-cell receptors. Cytotherapy; 5(3):211-226

Rapoport AP, Stadtmauer EA, Aqui NA, et al. (2005) Restoration of immunity in lymphopenic individuals with cancer by vaccination and adoptive T-cell transfer. Nat Med; 11(11):1230-1237

Roessig C, Scherer SP, Baer A, et al. (2002) Targeting CD19 with genetically modified EBV-specific human T lymphocytes. Ann Hematol; 81(2 Suppl):42S-43S

Russell JA, Walley KR, Singer J, et al. (2008) Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock. N Engl J Med; 358:877-887

Sadelain M, Riviere I, Brentjens R (2003) Targeting tumours with genetically enhanced T lymphocytes. Nat Rev Cancer; 3(1):35-45

Sant M, Allemani C, Tereanu C, et al. (2010) Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood; 116(19): 3724-3734

Serrano L, Pfeiffer T, Olivares S, et al. (2006) Differentiation of naïve cord-blood T cells into CD19-specific cytolytic effectors for post transplantation adoptive immunotherapy. Blood; 107(7):2643-2652

Sinn PL, Sauter SL, McCray PB (2005) Gene therapy progress and prospects: development of improved lentiviral and retroviral vectors-design, biosafety, and production. Gene Ther 12(14):1089-1098

Smith MA, Seibel NL, Altekruse SF, et al. (2010) Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol; 28: 2625-34

Stamenkovic I, Seed B (1988) CD19, the earliest differentiation antigen of the B cell lineage, bears three extracellular immunoglobulin-like domains and an epstein-barr virus-related cytoplasmic tail. J Exp Med; 168:1205-1210

Sullivan KM, Storb R, Buckner CD, et al. (1989) Graft-versus-host as adoptive immunotherapy in patients with advanced hematologic neoplasms. N Engl J Med; 320(13):828-834

Surh CD, Sprent J (2000) Homeostatic T cell proliferation: how far can T cells be activated to self-ligands? J Exp Med; 192(4):F9-F14 [Sullivan KM, Storb R, Buckner CD, et al. (1989)] Graft-versus-host as adoptive immunotherapy in patients with advanced hematologic neoplasms. N Engl J Med; 320(13):828-834

Tallen G, Ratei R, Kaspers G, et al. (2010) Long-term outcome in children with relapsed acute lymphoblastic leukemia after time-point and site-of-relapse stratification and intensified short-course multidrug chemotherapy: results of trial all-rez bfm 90. J Clin Oncol; 28(14):2339-2347

Tedder T, Isaacs C (1989) Isolation of cDNAs encoding the CD19 antigen of human and mouse B lymphocytes. A new member of the immunoglobulin superfamily. J Immunol; 143(2):717-717

[redacted]

Topp M, Gokbuget N, Stein A, et al. (2015) Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol; 16: 57-66

van der Veer A, Waanders E, Pieters R, et al. (2013) Independent prognostic value of *BCR-ABL1-like* signature and *IKZF1* deletion, but not high *CRLF2* expression, in children with B-cell precursor ALL. Blood; 122(15):2622-2629

van Stipdonk MJ, Lemmens EE, Schoenberger SP (2001) Naive CTLs require a single brief period of antigenic stimulation for clonal expansion and differentiation. Nat Immunol 2(5): 423-429

Weissert R (2011) Progressive multifocal leukoencephalopathy. J Neuroimmunology 231: 73-77

Willemsen RA, Weijtens MEM, Ronteltap C, et al. (2000) Grafting primary human T lymphocytes with cancer-specific chimeric single chain and two chain TCR. Gene Ther; 7:1369-1377

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14 Appendices

14.1 Appendix 1: Guidelines for efficacy evaluation in Acute Lymphoblastic Leukemia (ALL) studies

Document history

Version	Date	Changes
Draft v1.0	26-Jul-2013	First draft version for SPA
Draft v2.0	2-Dec-2013	Second draft version for SPA • CSF assessment by LP is required to establish CR or CRi for the first time • If there is extramedullary disease captured by physical exam, results will be classified by suspicion for leukemic involvement • Clarify the population for time to event variable analysis • For the analysis of DOR and other time to event endpoints, recommend to perform primary analysis by censoring SCT and sensitivity analysis by ignoring SCT • Add recommendation of sensitivity analysis of DOR considering death due to ALL as a competing risk • Clarify that for EFS patients who do not achieve complete response (CR or CRi) will be considered to have had an event on Day 1. Furthermore, patients who withdraw consent or are lost to follow-up will be censored in EFS analysis (rather than being considered to have had an event) • Other minor editorial changes
Draft v3.0	17-Jan-2014	Third draft version for SPA • Remove wording regarding acute lymphoblastic lymphoma because they will be excluded from the population to study • Revise wording regarding “clinical evidence of relapse” which is determined by peripheral blood assessment and extramedullary assessment (physical exam and CNS symptom assessment) • For the analysis of DOR, “death due to reason other than ALL” will be considered as a competing risk event for primary analysis
Draft v4.0	7-Mar-2014	Final version for SPA
Final v1.0	5-Mar-2014	First final version
Final v1.1	23-Dec-2014	Change the calculation of overall response date so that if the overall response classified as “No response”, the date of overall response will be calculated as the earliest of any component that reveals lack of response.
Final v1.2	26-Aug-2015	• Clarify that the qualitative assessment of tumor involvement will be used to determine response status when no blast count result is available from either bone marrow biopsy or aspirate. • Clarify that peripheral blood can be considered to be in remission status when bone marrow is in remission status at the same time. • Change the baseline disease assessment definition to indicate that the most current assessments within the protocol specified window will be used

[redacted]

Version	Date	Changes
Final v1.3	23-Feb-2016	• Remove the wording of Trilineage Hematopoiesis in the response assessment because the criteria for assessment, rigorous, and reproducible documentation of “trilineage hematopoiesis” in the marrow has not been well established. This can alternately be supported, in a reproducible and quantitative manner, by the use of peripheral blood platelet and neutrophil minimum values in the absence of transfusion of these blood components. • Change the baseline disease assessment definition to indicate that the most current assessment prior to enrollment/randomization will be used. Given the potentially long interval between enrollment and infusion of CTL019, more restricted time interval definition of baseline disease assessment is now implemented.

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List of abbreviations

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ASH	American Society of Hematology
CHMP	Committee for Medicinal Products for Human Use
CR	Complete remission
Cri	CR with incomplete blood count recovery
(e)CRF	(electronic) case report form
CSF	Cerebral spinal fluid
CT scan	Computed Tomography scan
DOR	Duration of response
EFS	Event-free survival
FDA	United States Food and Drug Administration
IWG	International Working Group
LP	Lumbar puncture
mcL	Micro liter
MNC	Mononuclear cells
MRD	Minimal residual disease
NCI-WG	National Cancer Institute-Working Group
NCCN	National Comprehensive Cancer Network
ORR	Overall remission rate
OS	Overall survival
PR	Partial remission
RAP	Report and Analysis Plan
RBC	Red blood cell
PQ-PCR	Real-time quantitative polymerase chain reaction
RFS	Relapse-free survival
SCT	Stem cell transplant
SPD	Sum of the product of the diameters
TOC	Table of Contents
TTR	Time to remission
WBC	White blood cell

[redacted]

14.1.1 Introduction

This document provides the working definitions and specifications for a consistent and efficient analysis of efficacy for CTL019 clinical studies assessing antineoplastic activity in adult and pediatric acute lymphoblastic leukemia (ALL). The current document is written primarily for the relapse and refractory disease setting. Modifications may be indicated for earlier disease settings.

This document is based on the standardized response criteria defined by National Comprehensive Cancer Network (NCCN) Guidelines (NCCN 2013 v1) and further supported by the workshop report on acute leukemia from American Society of Hematology (ASH) (Appelbaum et al 2007) and the International Working Group (IWG) guideline for acute myeloid leukemia (AML) (Cheson et al 2003).

The Cheson IWG guideline and Appelbaum ASH report were used in recent drug approvals (e.g. Marqibo) in ALL, prior to the NCCN guideline availability. The NCCN guidance is a more recently published United States based guideline for ALL.

The objectives of this document are to:

- Ensure that the definitions of responses in a clinical study protocol correctly reflect the above mentioned guidelines.
- Provide guidance for the response assessment and clinical monitoring to ensure consistency in applying the guidelines.

Moreover, this document describes data handling and derivation rules. Respective sections may be used in the report and analysis plan (RAP) to provide further details. Relevant sections of this document will be copied into individual clinical trial protocols as appendix to the protocol.

14.1.2 Efficacy evaluation

Efficacy assessments are based on bone marrow and blood morphologic criteria, physical examination findings, along with laboratory assessments of cerebral spinal fluid (CSF) and bone marrow minimal residual disease (MRD) assessment. Radiologic assessments are used only in specific settings as defined below. It needs to be clearly specified in the protocol which response categories are considered as primary. Selection criteria for choosing efficacy endpoints should reflect the study setting accordingly.

14.1.2.1 Types of efficacy assessments

Disease characterization at baseline and evaluation of response rely on the following:

- Bone marrow assessment
- Peripheral blood assessment
- Extramedullary disease assessment, including
  - CNS disease
  - Other extramedullary sites
- Minimal residual disease (MRD) assessment of bone marrow

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For timing and window of the disease assessments for response classification, see Section 14.1.2.3.1 for details.

14.1.2.1.1 Assessment of bone marrow blast counts

Bone marrow will be assessed for blast cells. Percentage of blast cells will be determined by morphologic or cytologic examination. This assessment can be performed on bone marrow biopsy and/or aspirate. If the blast counts are assessed, results from these assessments are considered to be interchangeable. Some laboratories do not perform differential counts on bone marrow biopsies, but rather provide a qualitative assessment whether there is tumor involvement or not: i.e. Yes or No tumor (blast) cells are seen in the bone marrow biopsy section or the touch print from the bone marrow biopsy. In this case, it may not be possible to definitively determine whether the blast count is <5% or not.

Both bone marrow biopsy and aspirate tests will be considered for response assessment as follows:

- In the case of only one assessment with non-missing blast count values: Result of the non-missing assessment will be used.
- In the case of both assessments with differing, non-missing blast count values: The highest blasts value will be considered. The corresponding assessment date will be used as reference for other assessments for the determination of evaluation windows.
- In the case of no blast count values available from either aspirate or biopsy, but a qualitative assessment of tumor involvement from biopsy is available: The bone marrow result will be considered to be in remission if there is no tumor involvement, and will be considered to indicate no response or relapsed disease if there is tumor involvement.
- In the case of no blast count values available from either aspirate or biopsy, and no qualitative assessment of tumor involvement from biopsy is available: The bone marrow result will be considered as “unknown”.

14.1.2.1.2 Assessment of peripheral blood

All values must be taken from the same blood sample. Relevant variables are platelet and neutrophil counts and percentage of leukemic blasts. Recent transfusion status also has to be taken into account (See Section 14.1.2.3.3 for details).

If the peripheral blood count is so low that a differential count cannot be obtained (e.g. typically when WBC < 0.5 x 10^9/L preventing an accurate assessment of differential count), but the bone marrow result is showing complete remission status (per definition in Table 14-1). In this case, the patient will also be considered to be in remission status in peripheral blood.

14.1.2.1.3 Assessment of extramedullary disease

Extramedullary involvement is to be assessed at baseline and at each visit for response assessment. Presence or absence and physical location of extramedullary disease is to be captured in the (e)CRF.

Extramedullary disease is to be assessed via physical examination, CSF assessment, and if clinically appropriate relevant imaging techniques. In case of extramedullary disease at

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baseline or (re-)appearance during the study, the lesions should be considered for confirmation by imaging or biopsy if technically and/or clinically feasible.

14.1.2.1.3.1 Assessment of CNS disease

Baseline CSF assessment by lumbar puncture (LP) is mandatory. The frequency and timing of post-baseline CSF assessment may depend upon the study setting and standard of care for each setting (e.g. front line or relapse/refractory, pediatric vs adult, etc.) and should be clearly specified in the protocol. At a minimum, lumbar puncture should be performed as clinically indicated by the presence of neurologic symptoms.

The classification of CNS status includes the following:

- CNS-1 refers to no lymphoblasts in the CSF regardless of WBC count;
- CNS-2 is defined as WBC less than 5/mcL in CSF with presence of lymphoblasts;
- CNS-3 is defined as WBC of 5/mcL or greater with presence of lymphoblasts.

If the patient has leukemic cells in the peripheral blood and the LP is traumatic and WBC ≥ 5/mcL in CSF with blasts, then compare the CSF WBC/RBC ratio to the blood WBC/RBC ratio. If the CSF ratio is at least two-fold greater than the blood ratio, then the classification is CNS-3; if not, then it is CNS-2.

CNS remission is defined as achievement of CNS-1 status in a patient with CNS-2 or CNS-3 at initial assessment.

CNS relapse is defined as development of CNS-3 status or development of clinical signs of CNS leukemia (e.g., facial nerve palsy, brain/eye involvement, hypothalamic syndrome, etc.). If clinical signs of CNS leukemia exist, it must be confirmed by CNS imaging (CT or MRI of brain) or other relevant methods (e.g. biopsy, LP, etc.) to define CNS relapse.

14.1.2.1.3.2 Assessment of mediastinal disease

Radiographic assessments are not standard components for routine disease assessments of acute lymphoblastic leukemia (NCCN 2013 v1, Cheson et al 2003).

The classification of mediastinal response in NCCN 2013 v1 based on radiographic assessments is hence not applicable for studies where only acute lymphoblastic leukemia patients are studied.

14.1.2.1.3.3 Assessment of other extramedullary disease

The assessment of other extramedullary disease (hepatomegaly, splenomegaly, skin/gum infiltration, testicular mass or other masses) will be performed via physical exam.

Hepatomegaly and splenomegaly due to leukemic involvement, disease involvement by lymph nodes, infiltration of the skin or gums, unilateral or bilateral testicular mass, or other masses will be assessed by physical exam. Results will be coded as “Normal”, “Abnormal with no or low suspicion for leukemic involvement”, or “Abnormal with high suspicion for leukemic involvement”. The rationale for these three categories is as follows. Other abnormalities that are not related to leukemic infiltration can often be observed in these organ sites on physical examination in patients with ALL, especially during the first 28 days after

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lymphodepleting chemotherapy followed by CTL019 cell infusion. Definitive proof of leukemic infiltration (e.g. liver biopsy) is often not definitive, indicated or ethically justified. Some abnormalities may occur (e.g. ecchymosis in skin or gums, acute/transient hepatosplenomegaly associated with acute infections or Macrophage Activation Syndrome (MAS)) but are clearly not leukemic involvement. Therefore three categories will more accurately capture these different clinical scenarios. In the analysis, "Normal" or "Abnormal with no or low suspicion for leukemic involvement" will be considered eligible for overall CR or CRi assessment; "Abnormal with high suspicion for leukemic involvement" will not be considered eligible for overall CR or CRi assessment, and will be considered to trigger relapsed disease assessment. Serial physical examinations for these assessments will be performed (at protocol specified frequency) to validate the persistence or resolution of such findings.

Lymph nodes on physical exam are considered to be abnormal if greater than 1.5 cm. Note that although the cutoff of 1.5 cm is not defined in the NCCN (NCCN 2013 v1) or the Cheson guidelines (Cheson et al 2003), it is used in the international harmonization project revised response criteria for lymphoma (Cheson (2007a) and Cheson (2007b)) and the international working group guideline for chronic lymphocytic leukemia (Hallek et al 2008).

14.1.2.1.4 Assessment of minimum residual disease (MRD) in bone marrow

MRD in ALL refers to the presence of leukemic cells below the threshold of detection using conventional morphologic methods. Patients who experienced a CR according to morphologic assessment alone can potentially harbor a large number of leukemic cells in the bone marrow: up to 10^{10} malignant cells which can confer a poor outcome. The most frequently used methods for MRD assessment include multicolor flow cytometry to detect abnormal immunophenotypes and PCR assays to detect clonal rearrangements in immunoglobulin heavy chain genes and/or T-cell receptor genes or fusion transcripts (e.g. BCR-ABL). Current flow cytometry or PCR methods can detect leukemic cells at a sensitivity threshold of fewer than 1×10^{-4} (<0.01%) bone marrow mononuclear cells (MNCs). The concordance rate for detecting MRD between these methods is high. Numerous studies in childhood and adult ALL have shown the prognostic importance of post-induction (and/or post-consolidation) MRD measurements in predicting the likelihood of disease relapse. The timing of MRD assessment varies depending on the ALL treatment protocol and the disease setting (e.g. initial/up front treatment vs relapse/refractory). For MRD evaluation on multicolor flow cytometry, sampling of bone marrow MNCs is preferred over peripheral blood samples. At least 1×10^6 MNCs are required for analysis (≈ 2 mL of bone marrow or 5–10 mL of peripheral blood provides sufficient number of cells for multiple analysis). For MRD evaluation with real-time quantitative PCR (RQ-PCR), sampling of bone marrow MNC is preferred. At least 1×10^7 MNCs are required for initial marker characterization and generation of individual dilution series; 1×10^6 MNCs are sufficient for follow-up analysis. The minimal limit of assay sensitivity (to declare MRD negativity) should be less than 1×10^{-4} (< 0.01%).

For Ph+ ALL, BCR-ABL quantitative PCR may also be used to assess MRD status.

The timing of MRD assessment is dependent upon the disease setting and should be specified in the protocol.

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MRD assessment by flow cytometry or RQ-PCR should be performed via a central certified lab with 0.01% sensitivity. MRD by deep sequencing should be considered as exploratory objective.

14.1.2.2 Baseline evaluation

The following baseline assessments are mandatory:

- Bone marrow biopsy and/or aspirate for blast cell counts (Section 14.1.2.1.1)
- Peripheral blood for blast, neutrophil and platelet cell counts (Section 14.1.2.1.2)
- CSF cytology via lumbar puncture for WBC, RBC cell and lymphoblast numbers (Section 14.1.2.1.3.1)
- CNS imaging (CT or MRI) or other appropriate assessment if clinical signs of CNS leukemia exist (Section 14.1.2.1.3.1)
- Physical exam for extramedullary disease (Section 14.1.2.1.3.3)
- Blood and bone marrow MRD assessment by flow cytometry (Section 14.1.2.1.4)
- Cytogenetics and/or FISH from bone marrow aspirate

For disease characterization at baseline, the most current assessments (bone marrow, blood count, CSF, physical exam, etc.) on or prior to the date of enrollment/randomization should be used as the baseline assessment.

14.1.2.3 Post-baseline overall disease response evaluation

14.1.2.3.1 Components and timing of overall disease response evaluation

The initial achievement of CR or CRi will require evaluation of remission in bone marrow, peripheral blood, and the absence of extramedullary disease. Following initial achievement of CR or CRi, if the patients have normal peripheral blood, physical exam and no CNS symptoms, they will be considered to remain in clinical CR or CRi, i.e. there is no clinical evidence of relapse (Section 14.1.2.3.4).

An overall disease response evaluation must consist all of the following components:

- Peripheral blood for morphologic blast, neutrophil and platelet cell counts (Section 14.1.2.1.2)
- CNS symptom assessment (Section 14.1.2.1.3.1)
- Physical examination for extramedullary disease (Section 14.1.2.1.3.3)

In addition,

- Post-baseline bone marrow biopsies and/or aspirates (Section 14.1.2.1.1) for morphologic blast cell counts are required to demonstrate that a patient has achieved CR or CRi for the first time. Following initial achievement of CR or CRi, a bone marrow biopsy or aspirate will not be required unless it is clinically indicated (e.g. worsening of platelet or neutrophils; reappearance of blast in peripheral blood, etc.) or as specified per individual protocol.
- Post-baseline CSF cytology via lumbar puncture (Section 14.1.2.1.3.1) is required to demonstrate that a patient has achieved CR or CRi for the first time. Following initial

[redacted]

achievement of CR or CRi, a lumbar puncture will not be required unless it is clinically indicated by the presence of neurologic symptoms and as specified per individual protocol.

- MRD assessment (Section 14.1.2.1.4) should be performed per protocol specification.

In order for all components of disease assessments to be qualified as the same response evaluation, peripheral blood sample collection, CNS symptom assessment, physical exam, bone marrow biopsy/aspirate (if needed) and lumbar puncture (if needed) need to be performed, in general, within 14 days of each other, unless specified otherwise in the protocol.

In case of missing data for the full evaluation required to qualify for a certain response category, the overall evaluation "unknown" will be assigned unless at least one observation was made which qualifies for relapse. Relapse can be determined by the relapsed component alone.

Also see Section 14.1.2.3.2 and Section 14.1.2.3.4 for the definition and confirmation of disease response.

The frequency of response evaluation for each component needs to be clearly specified in the protocol. The timing should be coordinated so that a full response evaluation can be made.

14.1.2.3.2 Response criteria

The overall disease response is determined at a given evaluation using the criteria described in Table 14-1. Note that:

- The NCCN guidance (NCCN 2013 v1) has defined a progressive disease (PD) category. In this document, PD is considered the same as "No response", which is consistent with Cheson et al (2003) guideline. The difference between PD and "No response" in ALL is not believed to be clinically meaningful.
- See Section 14.1.2.1.1 for details regarding assessing bone marrow response status.

[redacted]

Table 14-1 Overall disease response classification at a given evaluation time

Response category	Definition
Complete remission (CR)	All the following criteria are met: **Bone marrow** • < 5% blasts **Peripheral blood** • Neutrophils > 1.0 x 10^9/L, and • Platelets > 100 x 10^9/L, and • Circulating blasts < 1% **Extramedullary disease** • No clinical evidence of extramedullary disease (by physical exam and CNS symptom assessment) and • If additional assessments (e.g. CSF assessment by LP, CNS imaging, biopsy, etc.) are performed, results must show remission status **Transfusion independency** (see Section 14.1.2.3.3). • No platelet and/or neutrophil transfusions less than or equal to 7 days before the date of the peripheral blood sample for disease assessment
Complete remission with incomplete blood count recovery (CRi)	All criteria for CR as defined above are met, except that the following exist: • Neutrophils ≤ 1.0 x 10^9/L, and/or • Platelets ≤ 100 x 10^9/L, and/or • Platelet and/or neutrophil transfusions less than or equal to 7 days before the date of the peripheral blood sample for disease assessment
No response	Failure to attain the criteria needed for any response categories or relapse
Relapsed Disease	Only in patients who achieved a CR or CRi and who have: • Reappearance of blasts in the blood (≥ 1%), or • Reappearance of blasts in bone marrow (≥ 5%), or • (Re-)appearance of any extramedullary disease after CR or CRi
Unknown	"Unknown" is assigned in case the baseline assessment or the response assessment is not done, incomplete, indeterminate, or not performed within the respective time frame (Section 14.1.2.2 and Section 14.1.2.3.1). If there is evidence of relapse, the overall response will assessed as "relapsed disease" with the relapsed component alone.

14.1.2.3.3 Evaluation of transfusion dependency

Information on transfusion dependency will be assessed at baseline as well as during the course of the trial for all patients. Transfusion of blood products will be recorded in a separate module of the (e)CRF. The type of transfusion, start and end date as well as the volume of blood product will be captured at each visit with hematologic assessment.

A period of at least one week (7 days) without any transfusion has been taken as a convention to define the status of transfusion independence to assess a CR vs CRi response (Cheson et al 2006). Any sample of peripheral blood sample for disease assessment which was taken less than or equal to seven days after a transfusion will be considered as transfusion dependent.

14.1.2.3.4 Establishing CR/CRi and subsequent maintenance of CR/CRi with no clinical evidence of relapse

A full response evaluation, including assessments of peripheral blood, bone marrow, CNS symptoms, physical exam and CSF assessment by LP, is required at the first time a CR or CRi

[redacted]

is demonstrated (Section 14.1.2.3.1). Bone marrow biopsy/aspirate and CSF assessment by LP are required 1 month (Day 28) after infusion. If the patient is not in CR/CRi at Month 1, then a bone marrow biopsy/aspirate and CSF assessment by LP are also required at the first time clinical evidence of remission is seen by peripheral blood and extramedullary disease assessment (physical exam and CNS symptom assessment) to establish that a patient has achieved CR/CRi for the first time. Additional bone marrow biopsies/aspirates and CSF assessments by LP may be recommended in the protocol.

Complete remissions in patients with ALL have been observed to take place within 1 month after infusion with CTL019. The onset of complete remissions are rapid and dramatic, and patients quickly regain a normal performance status. ALL relapse in the bone marrow is rapidly followed by signs or symptoms of disease recurrence as well as abnormalities in the peripheral blood.

Therefore, following initial achievement of CR/CRi, patients will be considered to have maintained a clinical CR/CRi if the patient has no evidence of extramedullary disease (by physical exam and CNS symptom assessment) and circulating blasts in peripheral blood are <1%.

In order for the best overall disease response to be categorized as CR or CRi, there must be no clinical evidence of relapse as assessed by peripheral blood and extramedullary disease assessment (physical exam and CNS symptom assessment) at a minimum of 4 weeks (28 days) after the initial achievement of CR or CRi. Please note, if additional assessments (e.g. bone marrow, CSF assessment by LP, CNS imaging, biopsy, etc.) are performed (Section 14.1.2.3.1) in the same evaluation for disease response evaluation purpose, they will also need to show remission status.

The onset date of CR or CRi will then be derived as the evaluation date of the initial CR or CRi assessment. If a patient satisfied CRi at one evaluation and later confirmed as a CR in the next evaluation, the patient will be considered as having confirmed CR. However, the date of CR will be derived as the latter (confirmed) evaluation date.

14.1.2.3.5 Date of overall disease response evaluation

A complete evaluation of response includes at the minimum the assessments of peripheral blood, CNS symptoms and physical exam. In addition, bone marrow and CSF assessment may be required. All components of disease assessments must be performed within the specified time frame (Section 14.1.2.3.1) to be qualified as the same response evaluation.

If the overall disease response is CR, CRi, or Unknown, the evaluation date (i.e. for one evaluation number) is defined as the latest of all dates of required measurements at that evaluation number. This rule applies also in case of multiple measurements of the same variable.

Relapse or No response can be assessed based on a partial evaluation (e.g. a relapse is assessed from blood alone). The assessment date for relapse or no response is calculated as the earliest date of all assessments that reveal a relapse or lack of response.

[redacted]

14.1.3 Data collection

14.1.3.1 Data sources

The summary of data sources refers to disease-specific (e)CRF standard modules. It is not appropriate to deviate from these specifications in Table 14-2.

Table 14-2 Data sources

(e)CRF module	Specification
Overall disease response	Overall disease response and assessments of individual components from • bone marrow; • blood; • CNS disease; • other extramedullary disease.
Bone marrow biopsy / aspirate	Aspirate or biopsy; morphologic blast counts and MRD assessment.
Blood response	Response status for platelets, neutrophils, morphologic blast counts; status of platelet and/or neutrophils transfusion.
CSF assessment [1]	CSF lymphoblast, WBC, RBC
Other CNS disease	CNS symptoms, confirmation of CNS disease via imaging or other methods (if applicable)
Extramedullary disease by physical exam	Presence/absence, location, method of assessment, confirmation by biopsy or imaging or not if feasible
Blood component transfusions	Type and number of units of transfusions, timing with respect to disease assessment
Hematopoietic Stem Cell Transplant (SCT) – post infusion	Date, type of post-treatment SCT

[1] When there is clinical signs of CNS disease and/or at protocol specified time points

14.1.3.2 Recording response evaluation on the (e)CRFs

The components and timing needed to adequately assess overall disease response is outlined in Section 14.1.2.3.1. In practice, disease response evaluation (either a complete assessment or only some components) may be performed on both scheduled and unscheduled time points. Also it is not uncommon in oncology trials that disease responses are sometimes assessed at time points not matching the scheduled time points. For example, when a patient's condition prevents certain assessments, the scheduled evaluation will have to be delayed to a later time point.

As a result, the recording of response evaluation is aligned using the "Evaluation number" on the (e)CRFs. A new evaluation number should be assigned whenever a scheduled or unscheduled disease response assessment is performed, and hence is not necessarily aligned with the study visits.

When relapse can be judge based on any component. E.g. if a relapse is observed from blood sample alone without bone marrow assessment etc. at any time, it will be recorded on the (e)CRFs, with all other assessments as "not done" or "unknown".

See also Section 14.1.2.3.5 regarding assigning date of the overall response.

[redacted]

14.1.3.3 Capturing overall response evaluation

Data monitoring reports will be prepared to identify investigator's assessments which differ from calculated response based on the rules of this document. This discrepancy may be queried for clarification. However, the investigator's response will not be overruled in any case.

14.1.4 Efficacy analysis definitions

14.1.4.1 Local vs central evaluation of efficacy

The overall disease response at a given assessment may be provided from different sources:

- Investigator overall disease response based on local radiological assessments, local clinical, pathological (e.g. bone marrow) and laboratory response.
- Central review based on review of the totality of the source data by an independent review committee (IRC).

The Study Protocol should state which evaluation source will be used for the primary analysis.

14.1.4.2 Best overall disease response

The best overall disease response is the best disease response recorded from **randomization/first CTL019 infusion** until start of new anticancer therapy.

Best response will be assigned according to the following order:

1. CR
2. CRi
3. No response
4. Unknown

The best overall disease response for a patient is always calculated, based on the sequence of overall disease responses. For the best overall disease response to be categorized as CR or CRi, there must be no clinical evidence of relapse as assessed by peripheral blood and extramedullary disease assessment (physical exam and CNS symptom assessment) at a minimum of 4 weeks (28 days) after the initial achievement of CR or CRi, as explained in Section 14.1.2.3.4.

The overall remission rate (ORR) is defined as the proportion of patients with a best overall disease response of CR or CRi.

14.1.4.3 Time-to-event definitions

General rule for the calculation of the time to event interval is:

Time to event = event date - start date + 1 (in days)

When no post-baseline response assessments are available, the date of **randomization/first CTL019 infusion** will be used as event date when time is to be censored at last post-baseline response assessment, i.e. time to event variables will never be negative.

[redacted]

Often censoring time is determined based on date of adequate response assessment. Any response assessment is considered to be adequate if the assessment was performed and the outcome of the assessment was other than "unknown" or "not done".

14.1.4.3.1 Overall survival (OS)

Overall survival (OS) is the time from date of **randomization/ first CTL019 infusion** to the date of death due to any reason.

In case a patient is alive at the date of last contact on or before data cutoff, OS is censored at the date of last contact. The handling of SCT for the calculation of OS must be clearly specified in the protocol. See also Section 14.1.4.4 for more discussion.

OS will be assessed in all patients (FAS).

14.1.4.3.2 Duration of remission (DOR)

Duration of remission (DOR) is defined as the duration from the first documented onset of CRi or CR to the date of relapse or death due to ALL.

In case a patient does not have relapse or death due to ALL prior to data cutoff, DOR will be censored at the date of the last adequate assessment on or prior to the earliest censoring event. The censoring reason could be

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy
- Event after at least two missing scheduled disease assessment

In addition, death due to reason other than ALL can be considered as either a competing risk event to other events of interest (relapse or death due to ALL), or a censoring event. The protocol should clearly specify which analysis is used as the primary analysis for DOR.

Since patients in remission might choose to receive SCT, censoring due to SCT will overestimate the risk of relapse and therefore may be considered inappropriate for the main analysis, when there is a substantial number of patients choose to receive SCT (CHMP 2010). The handling of SCT for the calculation of DOR must be clearly specified in the protocol.

See also Section 14.1.4.4 for more discussion.

DOR will be assessed only in patients with the best overall response of CR or CRi.

14.1.4.3.3 Relapse-free survival (RFS)

Relapse-free survival (RFS) is measured by the time from achievement of CR or CRi whatever occurs first to relapse or death due to any cause during CR or CRi.

In case a patient does not have relapse or death due to any cause prior to data cutoff, RFS will be censored at the date of the last adequate assessment on or prior to the earliest censoring event. The censoring reason could be

- Ongoing without event

[redacted]

- Lost to follow-up
- Withdrew consent
- New anticancer therapy
- Event after at least two missing scheduled disease assessment

The handling of SCT for the calculation of RFS must be clearly specified in the protocol.

See also Section 14.1.4.4 for more discussion.

RFS will be assessed only in patients with the best overall response of CR or CRi.

14.1.4.3.4 Event-free survival (EFS)

Event-free survival (EFS) is the time from date of **randomization/first CTL019 infusion** to the earliest of the following:

- Death from any cause
- Relapse
- Treatment failure: Defined as no response in the study and discontinuation from the study due to any of the following reasons:
  - Adverse event (including abnormal laboratory values or abnormal test procedure results)
  - Lack of efficacy
  - New anticancer therapy

In case of treatment failure, the event date will be set to study Day 1 (CHMP 2010).

In case a patient does not experience an event (e.g. discontinuation as a result of withdrawal of consent, lost to follow-up, protocol violation or administrative problems) prior to data cutoff, EFS is censored at the last adequate response assessment date on or prior to the earliest censoring event. The censoring reason could be

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy
- Event after at least two missing scheduled disease assessment

The handling of SCT for the calculation of EFS must be clearly specified in the protocol.

See also Section 14.1.4.4 for more discussion.

EFS will be assessed in all patients (FAS).

14.1.4.4 Event and censoring date, sensitivity analyses

This section outlines the possible event and censoring dates for relapse (Table 14-3), addresses the issues of missing response assessments during the study, and the options for handling new anticancer therapy. It is important that the protocol and RAP specify the

[redacted]

primary analysis in detail with respect to the definition of event and censoring dates and also include a description of sensitivity analyses to be performed.

SCT is a standard treatment option for ALL patients. For time-to-event endpoints it needs to be specified in the protocol how patients who choose to undergo SCT following study protocol treatment will be handled for analysis.

Using the draft FDA guideline (2007) on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics) and the EMA guideline on the evaluation of Anticancer Medicinal Products in Man on Confirmatory studies in Haematological Malignancies (CHMP 2010) as references, the following analyses can be considered:

Table 14-3 Options for event dates used in DOR, EFS and RFS

Situation		Options for event date **(1) = default unless specified differently in the protocol or analysis plan**	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment	Censor
B	Relapse at scheduled assessment date or before next scheduled assessment	(1) Date of relapse	Event
		(2) Date of next scheduled assessment	Event
C1	Relapse after exactly one missing assessment	(1) Date of relapse	Event
		(2) Date of next scheduled assessment	Event
C2	Relapse after two or more missing assessments	(1) Date of last adequate assessment	Censor
		(2) Date of next scheduled assessment	Event
		(3) Date of relapse	Event
D	New anticancer therapy given (excluding SCT)	(1) Date of last adequate assessment	Censor
		(2) Date of secondary anti-cancer therapy	Censor
		(3) Date of secondary anti-cancer therapy	Event
		(4) N/A	Ignored
E	SCT	(1) Date of SCT	Censor
		(2) N/A	Ignored
		(3) Date of SCT	Competing Risk Event
		(4) Date of last adequate assessment prior to SCT	Censor
F	Death due to reasons other than ALL (for DOR only)	(1) Date of death	Competing Risk Event
		(2) Date of last adequate assessment	Censor

The primary analysis and the sensitivity analyses must be specified in the study protocol. Clearly define if and why options (1) are not used for situations, D and (if applicable) E.

Situations C (C1 and C2): Relapse or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual relapse or death date in the case of one missing assessment
- (C2) censoring at the date of the last adequate assessment in the case of two or more consecutive missing assessments

In the case of two or more missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity

[redacted]

analysis consists of backdating the event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation D: New anticancer therapy (excluding SCT) given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment prior to new anticancer therapy may be used as a default in this case.

Situation E: As SCT is an important treatment option in responding patients, it is appropriate to consider the date of SCT as censoring date, instead of censoring at the last tumor assessment date. However, censoring due to SCT will overestimate the rate of relapse and therefore may be considered inappropriate for the default analysis when a substantial number of patients choose to receive SCT. Analysis ignoring SCT should be considered (CHMP 2010).

Since SCT during remission after the experimental treatment may affect the risk of relapse, a sensitivity analysis may be considered in which SCT is regarded as a competing risk to the event of interest (e.g., relapse after the experimental treatment). In this analysis, the cumulative incidence function (CIF), instead of the usual KM, is used to estimate the probability of remaining free of the event of interest in the presence of the competing risk (Kim 2007).

Situation F: Note that the KM method used to analyze DOR in the presence of censoring can be biased if the censoring event is not independent to the event of interest (i.e. relapse and death due to ALL). Therefore, analysis can also be performed considering death due to reason other than ALL as a competing risk event. In this case, the cumulative incidence function (CIF) instead of KM is used to estimate the probability of relapse in the presence of the competing risk (Kim 2007).

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for response assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-3 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

Date of previous scheduled assessment (from baseline) is the date when a response assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate assessment.

The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and have to be specified in the study protocol or RAP documentation.

[redacted]

14.1.5 References (available upon request)

Appelbaum FR, et al. (2007) End points to establish the efficacy of new agents in the treatment of acute leukemia. Blood 109: 1810-1816

Cheson B, Bennet JM, Kopecky K, et al. (2003) Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. Journal of Clinical Oncology; 21(24):4642-9

Cheson BD (2007a) The international harmonization project for response criteria in lymphoma clinical trials. Hematol Oncol Clin N Am 21:841-854

Cheson BD, Greenberg P, Bennett J, et al. (2006) Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood; 108: 419-425

Cheson BD, Pfistner B, Juweid ME, et al. (2007b) Revised response criteria for malignant lymphoma. J Clin Oncol 25:579-586

CHMP (2010) Appendix 2 to the Guidance on the evaluation of anticancer medicinal products in man (CPMP/EWP/205/95 Rev. 3) on confirmatory studies in haematological malignancies

FDA Guideline (2007) Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007

Hallek M, et al. (2008) Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. Blood 111.12: 5446-5456

Kim H (2007) Cumulative Incidence in Competing Risks Data and Competing Risks Regression Analysis. Clinical Cancer Research 2007;13:559-565

National Comprehensive Cancer Network (NCCN) Guidelines (NCCN, 2013 v1), Acute Lymphoblastic Leukemia

[redacted]

14.2 Appendix 2: Eligibility based on serologic markers for hepatitis B infection

Table 14-4 Eligibility based on serologic markers for hepatitis B infection

Test	Results				
HBsAg	+	-	-	-	-
Anti-HBc	Any	+	-	+	-
Anti-HBs	Any	-	+	+	-
Eligibility	Not Eligible	Not Eligible	Eligible	Eligible	Eligible

If indeterminate results are obtained, viral DNA levels should be measured to confirm negative viral status.

HBsAg positive: Indicates active infection and/or chronic active and potential for reactivation with fulminant hepatitis. These patients are not eligible for this trial.

Anti-HBs positive: Protective – Indicates vaccination or previous infection that has been successfully resolved. These patients are eligible for this trial.

HBsAg negative, Anti-HBc positive, Anti-HBs negative: Indicates latent infection. These patients are also at risk for viral reactivation. These patients are not eligible for this trial.

[redacted]

14.3 Appendix 3: CTL019 modified data reporting – Treatment and Primary Follow Up Phase

14.3.1 Adverse event (AE) and serious adverse event (SAE) reporting

	Pre-treatment period (ICF to LD chemo/pre-infusion visit)	**Treatment Period** (Starting from LD chemo/pre-infusion visit)	**Post-treatment Period**
		Through Month 12 Visit	**After Month 12 Visit, through Month 60**
Non-serious Adverse Events (AE)	• Modified: • All infections • All laboratory abnormalities deemed clinically significant by the investigator • All clinical AEs grade ≥ 3 • All AEs related to a study procedure • All AEs leading to study discontinuation	All, including all laboratory abnormalities deemed clinically significant by the investigator	• Modified –Whether serious or non-serious, report following: • Events leading to death • Related to a study procedure • Infections • Serious or opportunistic infections. Defined as bacterial, viral, fungal or parasitic infections that fulfill one of the following criteria: Require anti-infective treatment OR Lead to significant disability or hospitalization OR Need surgical or other intervention • New incidence or exacerbation of a pre-existing neurologic disorder • New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder • New incidence of other hematologic disorder • Any severe adverse event or condition the investigator believes may have a reasonable relationship to CD19 CART therapy • Positive RCL test result • Vector insertion site sequencing result with a mono-or oligoclonality pattern or in a location near a known human oncogene • New malignancy (T-cell & non T-cell), other than the primary malignancy • Progressive multifocal leucoencephalopathy (PML) • Hepatitis B reactivation
Serious Adverse Events (SAE)	Modified: • All events leading to death • All events related to a study procedure • Any AE reportable for this study period that also meets criteria for serious • All pulmonary or cardiac abnormalities • All infections • Any substantial change in the status of the patient that precludes the patient from proceeding to study treatment (e.g. GVHD, rapid progression of malignancy, marked decline in performance status) • Any other substantial change in the status of the patient that the investigator deems may have a potential impact on the patients during lymphodepletion and CTL019 treatment	All	

[redacted]

14.3.2 Concomitant medication and laboratory reporting

	Pre-treatment period (ICF to LD chemo/pre-infusion visit)	**Treatment Period** (Starting from LD chemo/pre-infusion visit, through Month 12)		**Post-treatment Period** (After Month 12, through Month 60)
	Inpatient/ICU OR Outpatient	**Inpatient/ICU**	**Outpatient**	**Inpatient/ICU OR Outpatient**
Concomitant medications	Modified: **Drugs:** Record **all** of the following medications: • Anticytokine therapies (e.g. tocilizumab, or other) • Corticosteroids (including prophylactically for blood product administrations, physiologic replacement doses, high or stress doses, etc.) • Anti-seizure medications • Allopurinol, or non-allopurinol alternatives • Rasburicase • Immunoglobulin therapy • Any medication given therapeutically for an SAE • Vasopressors and cardiac inotropic agents (see below) • Narcotics and sedatives (see below) • Antineoplastic therapies (e.g. lymphodepeleting chemotherapy) • Related to an AE or SAE defined as reportable for this period **Vasopressors and cardiac inotropic agents:** • For dose, record only maximum daily rate (e.g. ug/kg/hr, mg/hr, etc.) **Narcotics and sedatives:** • For dose, record only total daily dose **Blood products (e.g. red cells, platelets, FFP, cryoprecipitate):** • **If administered ≤7 days of a tumor response assessment:** o Record ALL blood products, including prophylaxis (to distinguish CR vs CRi) • **If NOT administered ≤7 days of a tumor response assessment:** o Only record blood products if given for bleeding (excludes prophylactic use) • Related to an AE or SAE defined as reportable for this period **Electrolyte & vitamin replacement:** • Record all electrolyte replacement if given for a **≥ Grade 3** electrolyte disturbance		All	Modified: • Related to an AE or SAE defined as reportable for this period • Mutagenic agents (including cytotoxic drugs) • Radiation & antineoplastic therapy (including SCT) • Immunoglobulin therapy • Immunosuppressive agents (including dose of steroids higher than physiologic replacement therapy doses of steroids (< 12 mg/m2/day hydrocortisone or equivalent) • Investigational therapy

[redacted]

	Pre-treatment period (ICF to LD chemo/pre-infusion visit)	**Treatment Period** (Starting from LD chemo/pre-infusion visit, through Month 12)		**Post-treatment Period** (After Month 12, through Month 60)
	Inpatient/ICU OR Outpatient	**Inpatient/ICU**	**Outpatient**	**Inpatient/ICU OR Outpatient**
	and list these as an adverse event (AE). • Do **not** record ≤ Grade 2 or prophylactic use of electrolyte or vitamin replacements • Do **not** record total parenteral nutrition (TPN) on concomitant medication CRF **Fluids:** • Do **not** record fluid boluses and maintenance fluids			

Laboratory data	Modified:
	• Record **all** scheduled labs (per Visit Evaluation Schedule)
	• Record **all** results (scheduled or unscheduled) for: LDH, Uric acid, CRP, Ferritin, and fibrinogen (related to CRS/TLS/MAS)
	• Record all other laboratory values if they are ≥ Grade 3
	• For laboratory abnormalities reportable as AE/SAE, record laboratory results that support the event (scheduled or unscheduled)
	  • For any AE/SAE that may be caused by a laboratory abnormality, the laboratory value(s) (any grade) must also be recorded (e.g. “muscle cramps” potentially caused by hypokalemia)
	  • Laboratory abnormalities that are treated prophylactically are NOT to be recorded (e.g. maintenance electrolyte replacement, platelets given without clinical bleeding)
			All	Modified:
				• Record **all** scheduled labs (per Visit Evaluation Schedule)
				• Record **all** results (scheduled or unscheduled) for: LDH, Uric acid, CRP, Ferritin, and fibrinogen (related to CRS/TLS/MAS)
				• Record all other laboratory values if they are ≥ Grade 3
				• For laboratory abnormalities reportable as AE/SAE, record laboratory results that support the event (scheduled or unscheduled)
				  • For any AE/SAE that may be caused by a laboratory abnormality, the laboratory value(s) (any grade) must also be recorded (e.g. “muscle cramps” potentially caused by hypokalemia)
				  • Laboratory abnormalities that are treated prophylactically are NOT to be recorded (e.g. maintenance electrolyte replacement, platelets given without clinical bleeding)

[redacted]

14.4 Appendix 4: CTL019 modified data reporting – Secondary Follow Up Phase

Adverse Events/ Serious Adverse Events	Concomitant Medications
• New incidence or exacerbation of a pre-existing neurological disorder • New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder • New incidence of other hematologic disorders • Any severe adverse event or condition the investigator believes may have a reasonable relationship to CTL019 therapy • Any severe adverse event or condition that is unexpected • Positive RCL test result • Vector insertion site sequencing result with a mono-or oligoclonality pattern or in a location near a known human oncogene • New malignancy (T-cell & non T-cell), other than primary malignancy • Progressive multifocal leukoencephalopathy (PML) • Hepatitis B reactivation	• Intravenous Immunoglobulin

[redacted]

NOVARTIS

Clinical Development

CTL019 (tisagenlecleucel-T)

CCTL019B2202

A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia

Statistical Analysis Plan
Amendment 2

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1.1	21-May-2015	Draft for sDLT review, incorporating comments received from CTT
2.0	29-May-2015	Final version
3.0	16-Jul-2016	Amendment 1 Change file name to “Statistical Analysis Plan” following new RAP document naming convention. Protocol Amendment 2,3,4 Related updates: • Update the primary endpoint to be ORR within 3 months post CTL019 infusion instead of 6 months. • Add interim analysis with first 50 infused patients • Add analysis related to CTL019 manufactured at [redacted] • Add key secondary endpoints related to patients infused with CTL019 from US manufacturing facility • Revise the order of main and additional analysis for DOR to be consistent with the protocol • Update samples size calculation • Update details w.r.t. PRO analysis and healthcare resource utilization • Update the visit schedule and primary follow-up length; added summary of duration of study follow-up • Update efficacy baseline definition • Update response status category at study entry • Update AESI search criteria • Update analysis time window • Add summary plan for relapsed patients: site of initial relapse; CD19 status at initial relapse. • Add analysis about CR/CRI with MRD negative at day 28 • Update subgroup analysis plan Related to CSPD discussion • Update analysis for hematopoietic cytopenia • Update analysis of CRS and anti-cytokine therapies • Update PK analysis plan • Update analysis plan for B- and T- cells • Update analysis plan for apheresis product Details/Clarification for Programming • Update growth data analysis plan • Update partial data imputation rule

Version	Date	Changes
		• Update reference table • Definition of treatment failure • Definition of Enrolled set: add 'clinical' to the inclusion/exclusion criteria • Update PK language about imputation of non-quantifiable values; and values with status showing not reliable • Algorithm for censoring after missing two scheduled assessment • Add baseline B cell phenotype and CD19 expression summary • Other minor editorial changes and clarifications
4.0	15-Oct-2016	Amendment 2 • Add summary of post-infusion bleeding and cardiac events, regardless of study drug relationship, by group term, preferred term, and maximum grade in Section 4.7.2.2 • Other minor editorial changes and clarifications

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALL	Acute Lymphoblastic Leukemia
ATC	Anatomic Therapeutic Chemical (Classification)
AUC	Area Under the Curve
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CIF	Cumulative Incidence Function
Cmax	Maximum concentration
CNS	Central Nervous System
CR	Complete remission
CRi	Complete remission with incomplete blood count recovery
CRO	Contract Research Organization
CRP	C-Reactive Protein
CRS	Cytokine Release Syndrome
CSF	Cerebral Spinal Fluid
CTC	Common Toxicity Criteria
DNA	Deoxyribonucleic Acid
DOR	Duration of Remission
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EFS	Event Free Survival
FAS	Full Analysis Set
GVHD	Graft versus Host Disease
IEAS	Interim efficacy analysis set
IL	Interleukin
IRC	Independent Review Committee
KM	Kaplan Meier
LLOQ	Lower Limit of Quantification
LOQ	Limit of Quantification
MRD	Minimal Residual Disease
ORR	Overall Remission Rate
OS	Overall Survival
PD	Pharmacodynamics
PK	Pharmacokinetics

PPS	Per-Protocol Set
q-PCR	Quantitative Polymerase Chain Reaction
RFS	Relapse Free Survival
SCT	Stem Cell Transplantation
SDS	standard deviation score
Tmax	Time to peak concentration
ULOQ	Upper Limit of Quantification

1 Introduction

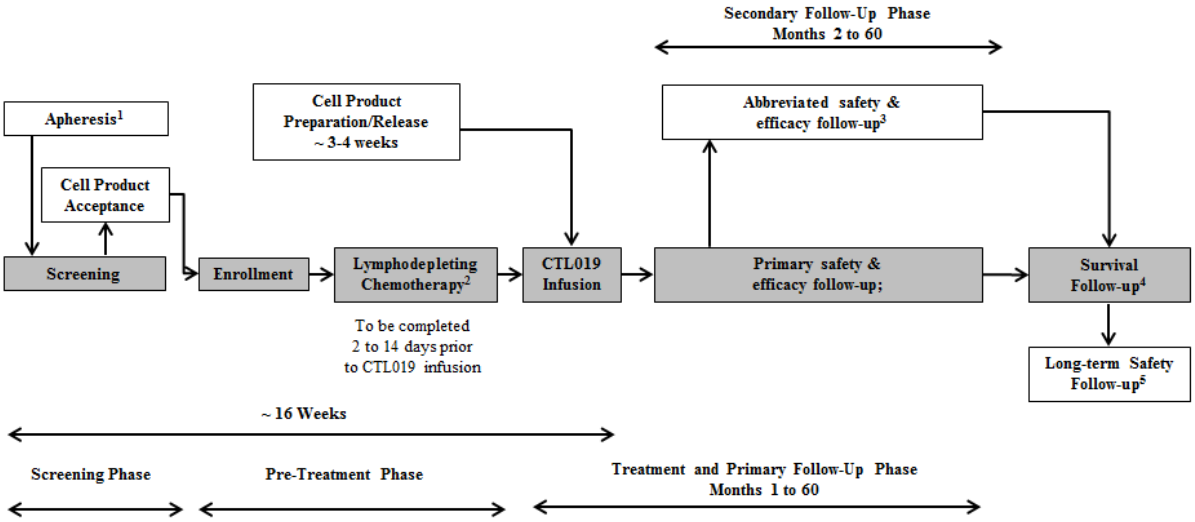
This document describes the detailed statistical methodology for the study CTL09B2202: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. The data will be analyzed by Novartis and/or a designated CRO. It is planned that the data from all centers that participate in this protocol will be used.

2 Study design, objectives and endpoints

2.1 Study Design

The target population for this study consists of pediatric patients with B-cell ALL who are refractory, relapsed after allogeneic SCT, or are otherwise ineligible for allogeneic SCT. The study will have the following sequential phases for all patients (see Figure 2-1): Screening, Pre-Treatment (cell product preparation and lymphodepleting chemotherapy), Treatment and Primary Follow-up (60 months), Secondary Follow-up, and Survival Follow-up. The total duration of the study is 5 years.

Figure 2-1 Study design



1 Performed prior to Study Entry
2 As indicated per protocol
3 Only for patients who drop out of the Primary Follow-up before Month 60.
4 Patients will be followed for survival until the end of trial, or until they are enrolled in the long-term follow-up.
5 Long term safety follow-up conducted per health authority guidance under a separate protocol

Only following informed consent/assent and confirmation of all clinical eligibility criteria will the patient's apheresis product be shipped to the manufacturing facility. The manufacturing facility will then evaluate the patient's apheresis product for acceptance. Enrollment is defined as the point at which a patient meets all clinical inclusion/exclusion criteria and the patient's apheresis product is received and accepted by the manufacturing facility.

Following enrollment, lymphodepleting chemotherapy may be started approximately one to three weeks before CTL019 infusion. The purpose of the chemotherapy is to induce lymphopenia in order to facilitate engraftment and homeostatic expansion of CTL019 cells. If patients have a White Blood Cell (WBC) count ≤ 1,000 cells/μL within one week prior to CTL019 infusion, lymphodepleting chemotherapy is not required.

CTL019 infusion will be given 2 to 14 days after completion of lymphodepleting chemotherapy , if lymphodepleting chemotherapy is required. A single dose will be administered. The target cell dose range is 2.0 to 5.0 x 10^6 autologous CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 1.0 to 2.5 x 10^8 autologous CTL019 transduced viable T cells (for patients > 50 kg). The allowable infused cell dose range of CTL019 transduced cells have been defined as 0.2 to 5.0 x 10^6 autologous CTL019 transduced viable T cells per kg body weight (for patients ≤ 50 kg) and 0.1 to 2.5 x 10^8 autologous CTL019 transduced viable T cells (for patients > 50 kg). CTL019 products below these minimum transduced cell doses will not be released for infusion.

After CTL019 infusion, efficacy will be assessed monthly for the first 6 months, then quarterly up to 2 years and semi-annually afterwards up to 5 years, or until patient relapse based on the Novartis guidelines for response assessment in ALL (Appendix 1 of protocol), which is based on NCCN version 1.2013 guidelines, Cheson et al (2003) and Appelbaum et al (2007). For patients who discontinued from primary follow-up while in remission, relapse status will be obtained every 3 months in the secondary follow-up until first relapse (if applicable). Safety will be assessed throughout the study. A post-study follow-up for lentiviral vector safety will continue under a separate destination protocol for 15 years post infusion per health authority guidelines.

The end of study is defined as the last patient's last visit (LPLV), which is the last patient's Month 60 evaluation (End of Treatment and Primary Follow-Up or End of Secondary Follow-up visit), or the time of premature withdrawal.

Patients may continue to be followed under the current protocol for relapse and survival until LPLV or until they choose to enroll into the 15 year long term follow-up protocol, whichever occurs first. Once a discontinued patient relapses, the patient will only be followed for survival. The relapse and survival follow-ups can be conducted in the form of telephone contact.

2.2 Study objectives and endpoints

Objectives and related endpoints are provided in Table 2-1 and detailed in the study protocol.

Table 2-1 Study objectives and endpoints

Objective	Endpoint
Primary	
Evaluate the efficacy of CTL019 therapy from all manufacturing facilities as measured by overall remission rate (ORR) during the 3 months after CTL019 administration, which includes CR and CR with incomplete blood count recovery (CRi) as determined by IRC assessment	ORR (= CR + CRi); See Protocol Appendix 1 for response definition
Key secondary	
Evaluate the efficacy of CTL019 therapy from US manufacturing facility as measured by overall remission rate (ORR) during the 3 months after CTL019 administration, which includes CR and CR with incomplete blood count recovery (CRi) as determined by IRC assessment	ORR (= CR + CRi) assessment; See Appendix 1 for response definition
Evaluate the percentage of patients who achieve a best overall response (BOR) of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry among all patients who receive CTL019 from all manufacturing facilities	Percentage of patients with BOR of CR or CRi with MRD negative bone marrow by flow cytometry during the 3 months after CTL019 infusion among all patients who are infused with CTL019 from all manufacturing facilities
Evaluate the percentage of patients who achieve a best overall response (BOR) of CR or CRi with a MRD negative bone marrow by central analysis using qPCR among patients who receive CTL019 from US manufacturing facility	Percentage of patients with BOR of CR or CRi with MRD negative bone marrow by qPCR during the 3 months after CTL019 infusion among all patients who are infused with CTL019 from US manufacturing facility
Other secondary	
Evaluate the percentage of patients who achieve CR or CRi at Month 6 without stem cell transplant (SCT) between CTL019 infusion and Month 6 response assessment	Percentage of patients who achieve CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment
Evaluate the percentage of patients who achieve CR or CRi and then proceed to SCT while in remission before Month 6 response assessment Evaluate the duration of remission (DOR)	• Percentage of patients who achieve CR or CRi and then proceed to SCT while in remission prior to Month 6 response assessment • In addition, all patients that proceed to SCT after CTL019 infusion will be described • DOR, i.e. the time from achievement of CR or CRi, whichever occurs first, to relapse or death due to ALL • Site of involvement of subsequent relapse will be summarized

Objective	Endpoint
Evaluate the relapse-free survival (RFS)	RFS, i.e. the time from achievement of CR or CRi whichever occurs first to relapse or death due to any cause during CR or CRi
Evaluate the event-free survival (EFS)	EFS, i.e. the time from date of CTL019 infusion to the earliest of death, relapse or treatment failure
Evaluate the overall survival (OS)	OS, i.e. the time from date of CTL019 infusion to the date of death due to any reason
Evaluate the response at Day 28 +/- 4 days	Proportion of patients attaining CR or CRi at Day 28 +/- 4 days post CTL019 infusion
Evaluate the impact of baseline tumor burden on response	Response as a function of baseline tumor burden (tumor load) (MRD, extramedullary disease, etc)
Evaluate the quality of response using MRD disease assessments before treatment, and at day 28 +/- 4 days after treatment using central assessment by qPCR and before SCT by local assessment (flow or PCR)	MRD quantitative result (% leukemic cells) and qualitative result (positive/negative)
Evaluate the safety of CTL019 therapy	Type, frequency and severity of adverse events and laboratory abnormalities
Characterize the *in vivo* cellular pharmacokinetic (PK) profile (levels, persistence, trafficking) of CTL019 cells in target tissues (blood, bone marrow, cerebral spinal fluid, and other tissues if available)	- q-PCR detected DNA encoding anti-CD19 chimeric antigen receptor (CTL019) in blood, bone marrow and CSF - Cmax, Tmax, AUCs and other relevant PK parameters of CTL019 in blood, bone-marrow, CSF if available - Persistence of CTL019 in blood, bone marrow and CSF (if available) (e.g. Mean Residence Time [MRT] last)
Describe the incidence of newly acquired and confirmed immunogenicity to CTL019	- Incidence of newly acquired and confirmed immunogenicity and anti-CTL019 assay titers
Describe the effect of CTL019 therapy on Patient Reported Outcomes (PRO)	PRO as measured by PedsQL and EQ-5D questionnaires
Derivation of a score to predict cytokine release syndrome	Develop a score utilizing clinical and biomarker data and assess its ability for early prediction of cytokine release syndrome
Describe the profile of soluble immune factors that may be key to cytokine release syndrome	Frequent monitoring of concentrations of soluble immune factors in blood
Describe the levels of B and T cells (peripheral blood and bone marrow) prior to and following CTL019 infusion for safety monitoring	Lymphocyte subsets of B and T cells and description of associated safety events
Assess the efficacy, safety and in vivo cellular pharmacokinetics of patients infused with CTL019 manufactured by [redacted]	- ORR and MRD negative remission - Type, frequency and severity of adverse events and laboratory abnormalities - CTL019 transgene levels by qPCR in blood, bone marrow and CSF if available
Exploratory	

Objective	Endpoint
Determine the incidence and pattern of tumor clonal evolution	- [redacted]
T cell trafficking (CTL019 immunophenotyping)	- CTL019 positive T cells and other leukocyte subsets
Describe the effect of anti-cytokine therapy on CRS, CTL019 PK/PD, and disease response	- Clinical CRS adverse events and laboratory measures of CRS (e.g. IL-6, , CRP, and ferritin concentrations) by anti-cytokine therapy - CTL019 concentrations and B cell depletion by anti-cytokine therapy - Disease response by anti-cytokine therapy
Quantify the relationship between 1) CTL019 cell product/apheresis product gene expression profiles 2) other cell product/apheresis product characteristics and clinical endpoints (efficacy, safety, PK)	- [redacted] - Apheresis and cell product characteristics [redacted] - Clinical response (CR, CRi, relapse) - MRD and B cell recovery assay results - PK parameters - CRS status - Cytokine response
To explore the relationship between CRS and initial tumor burden, clinical tumor response, and PK/PD parameters	- CRS occurrence, CRS grade, need for anti-cytokine therapies - Baseline tumor burden - Maximum clinical response - CTL019 concentrations and B cell depletion
[redacted]	[redacted]
Describe hospital resource utilization	- Number of patients with hospitalized infusion, total number of hospitalizations, and length of stay

3 Definitions and general methodology

3.1 Definitions

3.1.1 Study follow-up

Study follow-up consists of treatment and primary follow-up and secondary follow-up (if applicable).

After CTL019 infusion, patients are followed in the "treatment and primary follow-up phase" for up to 60 months for disease response assessment (blood, bone marrow and extramedullary disease etc.) and safety. When patient is unable to be followed in the primary follow-up phase, the patient will enter a secondary follow-up phase with reduced data collection schedule to collect remission/relapse information and health authority requested data (e.g. delayed adverse events, etc.). It is anticipated that patients may leave the primary follow-up and move to secondary follow-up due to reasons including: treatment failure, relapse after remission, pursuing SCT while in remission, or withdrawal from the primary follow-up (see protocol Section 7.1).

The end of primary follow-up will be refer to completion or discontinuation date of the treatment and primary follow-up phase. The study follow-up completion or discontinuation date will be refer to the completion/discontinuation date of the last phase (i.e. treatment and primary follow-up or secondary follow-up) the patient has entered.

3.1.2 Study drug and study treatment

Study drug is defined as CTL019 transduced cells.

Study treatment includes not only the study drug, i.e., CTL019 transduced cells, but also lymphodepleting chemotherapy.

3.1.3 Date of first administration of lymphodepleting chemotherapy

The date of first administration of lymphodepleting chemotherapy is defined as the first date when a non-zero dose of chemotherapy was administered and recorded on the “Concomitant Antineoplastic Therapy” electronic Case Report Form (eCRF) for the indication “Lymphodepleting”.

3.1.4 Date of infusion of study drug

The date of infusion of study drug is defined as the date when a non-zero dose of study drug (CTL019 transduced cells) was administered and recorded on the “Dosage administration record” eCRF.

3.1.5 Date of first study treatment

For patients who received lymphodepleting chemotherapy, the date of first study treatment is the date of first administration of lymphodepleting chemotherapy (as defined in Section 3.1.3);

for patients who did not receive lymphodepleting chemotherapy, the date of first study treatment is the date of infusion of study drug (as defined in Section 3.1.4).

3.1.6 Study day

The study day will be calculated as the difference between the date of the assessment and the date of first infusion of CTL019 (**Day 1**) plus 1 for assessments on or after the date of first infusion. For assessment before the date of first infusion, the study day will be calculated as the difference between the date of the assessment and the date of first infusion of CTL019 (**Day 1**) *(Note: if an event happens before the first day of CTL019 infusion then the study day will be negative.)* For patients who did not receive CTL019 infusion, their study days will not be calculated.

The study day will be displayed in all relevant data listings.

3.1.7 Baseline

For ***baseline disease evaluations***, the most current assessments (bone marrow, blood count, CSF, physical exam, etc.) on or prior to the date of enrollment will be used as the baseline assessment.

In the case that both bone marrow aspirate and biopsy morphological results are available the highest blasts value will be considered, and the corresponding assessment date will be used as reference for other assessments.

For ***safety evaluations*** (i.e. laboratory and vital signs), the last available assessment before CTL019 infusion is taken as 'baseline' values.

If patients have no value as defined above, the baseline results will be missing.

3.1.8 Last contact date

The last contact date will be used for censoring of patients in the analysis of overall survival.

For patients not known to have died as of the analysis cut-off date, the last contact date should be derived as the latest date on or before the data cut-off date from the dates listed in the first column of Table 3-1Last contact date data sources. For each of the sources specific conditions listed in the second column of Table 3-1 have to be fulfilled to ensure that there was true contact with the patient.

No additional dates are allowed to be used, e.g. dates coming from concomitant medications, PRO, etc.

Table 3-1 Last contact date data sources

Source data	Conditions
Last date patient was known to be alive from Survival Follow-up page	No condition
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End dates from drug administration record	Non-missing dose.

Source data	Conditions
Any specific efficacy assessment date if available	Evaluation is not missing.
Laboratory/PK collection dates	Sample collection with non-missing value.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

Note: completely imputed dates will not be used to derive the last contact date. Partial date's imputation is allowed to be used for event (death) and for censoring date only if coming from Survival Follow-up eCRF page (see Section 5.5.6 for details).

3.1.9 Lost to follow-up

For overall survival analysis, patients will be considered as lost to follow-up if the time between their last contact date and the analysis cutoff date is greater than or equal to 105 days (i.e., 3 months plus 2 weeks, assuming 1 month = 30.4375 days).

For response related time to event analysis (i.e. DOR, RFS and EFS), patients will be considered as lost to follow-up if the patient discontinued the study due to lost to follow-up.

3.2 Data Included in the analysis

Data from all participating centers will be combined.

An interim analysis will be performed when the first 50 patients who receive CTL019 have completed 3 months follow-up from study day 1 infusion or discontinued earlier. At the time of this interim analysis, assessment of all endpoints will be based only on patients who receive CTL019 manufactured from US manufacturing facility because there will be no patients treated with CTL019 manufactured from other manufacturing facilities.

The final analysis of the primary endpoint will be performed after all patients infused with CTL019 have completed 3 months from study day 1 infusion or discontinued earlier.

Selected efficacy and safety analysis will be updated annually afterwards. A final Clinical Study Report (CSR) will be produced once all patients complete or discontinue from the study.

3.3 Definitions of analysis sets

The analysis sets to be used are defined as below. The Interim efficacy analysis set (IEAS) and the Full analysis set (FAS) will be used as the primary efficacy analysis set for the interim and final analysis respectively. The Safety Set will be used for all safety analyses, unless otherwise specified. The Pharmacokinetic analysis set (PAS) will be used for pharmacokinetics analyses.

All tables and listings will be presented by one treatment arm of CTL019, unless otherwise specified.

Screened Set

The Screened Set comprises all patients who have signed informed consent/assent and screened in the study.

Enrolled Set

The Enrolled Set comprises all patients who are enrolled in the study. Enrollment date is defined as the point at which the patient meets all clinical inclusion/exclusion criteria, and the patients' leukapheresis product is received and accepted by the manufacturing facility. In case of protocol deviation such that patients are enrolled without meeting all inclusion/exclusion criteria, such patients will still be considered in the Enrolled Set, if the patients' leukapheresis product is received and accepted by the manufacturing facility.

Full Analysis Set (FAS)

The Full Analysis Set comprises all patients who received infusion of CTL019.

Interim Efficacy Analysis Set (IEAS)

At the time of interim analysis, the Interim Efficacy Analysis Set comprises the first 50 patients who receive CTL019 infusion.

Safety Set

The Safety Set comprises all patients who received infusion of CTL019. Note that the Safety Set and FAS are the same for this study.

Per-Protocol Set (PPS)

The Per-Protocol Set consists of a subset of the patients in the IEAS or FAS (at time of interim and final analysis respectively) who are compliant with major requirements of the study protocol.

Major protocol deviations leading to exclusion from the PPS include:

- Diagnosis of disease other than ALL at baseline;
- Prior therapy does not match with study protocol requirements in terms of number and types of previous therapy regimens;
- Missing or incomplete documentation of disease at baseline;
- CTL019 T-cells was infused to patients without fulfilling either of the following two conditions: (A) meeting all approved manufacturing release criteria; (B) released through exceptional release.

In addition, patients who receive a dose less than the minimum target dose of 2.0×10^6/kg (for patients ≤50 kg) or 1.0×10^8 (for patients >50 kg) CTL019 transduced viable T cells will also be excluded.

Pharmacokinetic Analysis Set (PAS)

The pharmacokinetic analysis set consists of a subset of IEAS or FAS (at time of interim and final analysis respectively) patients who have at least one sample providing evaluable PK data (i.e., samples not flagged for exclusion by the clinical pharmacologist) for CTL019. The PAS will be used for summaries (tables and figures) of PK data, and listings will be provided based on FAS. For any correlation analysis between PK data and other efficacy/safety endpoints, the PAS will be used.

Note that patients will be removed from the estimation of certain PK parameters on an individual basis depending on the number of available samples. These patients will be identified at the time of the analyses.

3.4 Response evaluation for ALL

3.4.1 Response criteria

The ALL response guideline is outlined in the Protocol Appendix 1 - Guidelines for efficacy evaluation in Acute Lymphoblastic Leukemia studies.

The overall disease response is determined at a given evaluation using the criteria described in Table 3-1Last contact date data sources below.

Table 3-2 Overall disease response classification at a given evaluation time

Response category	Definition
Complete remission (CR)	All the following criteria are met: **Bone marrow** • < 5% blasts **Peripheral blood** • Neutrophils > 1.0 x 10^9/L, and • Platelets > 100 x 10^9/L, and • Circulating blasts < 1% **Extramedullary disease** • No clinical evidence of extramedullary disease (by physical exam and central nervous system (CNS) symptom assessment), and • If additional assessments (e.g. CSF assessment by lumbar puncture (LP), CNS imaging, biopsy, etc.) are performed, results must show remission status **Transfusion independency** • No platelet and/or neutrophil transfusions less than or equal to 7 days before peripheral blood sample for disease assessment
Complete remission with incomplete blood count recovery (CRi)	All criteria for CR as defined above are met, except that the following exist: • Neutrophils ≤ 1.0 x 10^9/L, and/or • Platelets ≤ 100 x 10^9/L, and/or • Platelet and/or neutrophil transfusions less than or equal to 7 days before peripheral blood sample for disease assessment

Response category	Definition
No response	Failure to attain the criteria needed for any response categories or relapse
Relapsed Disease	Only in patients with a CR or CRi and who have: • Reappearance of blasts in the blood (≥ 1%), or • Reappearance of blasts in bone marrow (≥ 5%), or • (Re-)appearance of any extramedullary disease after CR or CRi
Unknown	"Unknown" is assigned in case the baseline assessment or the response assessment is not done, incomplete, indeterminate, or not performed within the respective time frame. If there is evidence of relapse, the overall response will assessed as "relapsed disease" with the relapsed component alone.

3.4.2 Establishing CR/CRi and subsequent maintenance of CR/CRi with no clinical evidence of relapse

A full response evaluation, including assessments of peripheral blood, bone marrow, CNS symptoms, physical exam and CSF assessment by LP, is required at the first time a CR or CRi is demonstrated. If the patient is not in CR/CRi at Month 1, then a bone marrow biopsy/aspirate and CSF assessment by LP are also required at the first time clinical evidence of remission is seen by peripheral blood and extramedullary disease assessment (physical exam and CNS symptom assessment) to establish that a patient has achieved CR/CRi for the first time. Additional bone marrow biopsies/aspirates and CSF assessments by LP may be recommended in the protocol.

Complete remissions in patients with ALL have been observed to take place within 1 month after infusion with CTL019. The onset of complete remissions is rapid and dramatic, and patients quickly regain a normal performance status. ALL relapse in the bone marrow is rapidly followed by signs or symptoms of disease recurrence as well as abnormalities in the peripheral blood.

Therefore, following initial achievement of CR/CRi, patients will be considered to have maintained a clinical CR/CRi if the patient has no evidence of extramedullary disease (by physical exam and CNS symptom assessment) and circulating blasts in peripheral blood are <1%.

In order for the best overall disease response to be categorized as CR or CRi, there must be no clinical evidence of relapse as assessed by peripheral blood and extramedullary disease assessment (physical exam and CNS symptom assessment) at a minimum of 4 weeks (28 days) after the initial achievement of CR or CRi. Please note, if additional assessments (e.g. bone marrow, CSF assessment by LP, CNS imaging, biopsy, etc.) are performed in the same evaluation for disease response evaluation purpose, they will also need to show remission status.

The onset date of CR or CRi will then be derived as the evaluation date of the initial CR or CRi assessment.

3.4.3 Date of overall disease response evaluation

A complete evaluation of response includes at the minimum the assessments of peripheral blood, CNS symptoms and physical exam. In addition, bone marrow and CSF assessment may be required. All components of disease assessments must be performed within the specified time frame (See Protocol Appendix 1) to be qualified as the same response evaluation.

If the overall disease response is CR, CRi or Unknown, the evaluation date (i.e. for one evaluation number) is defined as the latest of all dates of required measurements at that evaluation number. This rule applies also in case of multiple measurements of the same variable.

Relapse or No response can be assessed based on a partial evaluation (e.g. a relapse is assessed from blood alone). The assessment date for relapse or no response is calculated as the earliest date of all assessments that reveal a relapse or lack of response.

3.5 Time-to-event definitions

General rule for the calculation of the time to event interval is:

Time to event = event date - start date + 1 (in days)

When no post-baseline assessments of the event are available, the date of CTL019 infusion will be used as end date when time is to be censored at last post-baseline assessment of event, i.e. time to event variables will never be negative.

Often censoring time is determined based on date of adequate response assessment. Any response assessment is considered to be adequate if the assessment was performed and the outcome of the assessment was other than “unknown” or “not done”.

4 Statistical methods used in reporting

4.1 General presentation of descriptive summaries

Categorical data (e.g., gender, race, etc.) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

Continuous data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum).

4.2 Patient disposition

Patient disposition will be summarized for the following: screening phase for the Screened Set, pre-treatment phase for the Enrolled Set, treatment and primary follow-up phase and secondary follow-up phase for the FAS. The patient disposition for each phase will be summarized for all patients who entered that phase. The number and percentage of patients in each of the categories as listed for “End of Phase Disposition eCRF” pages will be tabulated and listed. Patients who have entered any study phase but have not completed/discontinued will be listed as appropriate.

For the screening phase, the clinical eligibility criteria that were not met by patients will also be tabulated. In addition, the number and percentage of patients who enrolled in the long term follow-up study will be summarized.

In addition, a high level disposition summary including all phases will be provided for all screened patients.

Duration of primary follow-up and total duration of study follow-up will be summarized numerically as well as by categories: <6 months, 6 months to <12 months, 12 months to <24 months, >=24 months.

4.3 Background and demographic characteristics

The FAS (as well as the IEAS at interim analysis) will be used for all baseline disease characteristics and demographic summaries. The Enrolled Set will be used for listings, where patients will be presented by whether they have received CTL019 or not.

4.3.1 Basic demographics data

Demographic and other baseline data will be listed by patient and/or summarized descriptively.

4.3.2 Medical history and ALL disease characteristics

Medical history and ongoing conditions, including cancer-related conditions and symptoms at the time of informed consent will be summarized and listed. Ongoing and historical medical conditions will be flagged separately in the listing. The summaries will be presented by primary system organ class and preferred term. Medical histories are coded using the medical dictionary for regulatory activities (MedDRA) terminology.

The CD19 status, MRD status by central assessment, local morphologic blast count, CNS classification and other extramedullary disease status prior to enrollment will be summarized.

Number and percentage of patients with CNS involvement by ALL at any time prior to enrollment will be summarized.

Other CNS disease history (usually non-leukemic, see Section 5.8) and CNS related prior radiotherapy (e.g. to the brain or cranial spinal axis) will also be summarized.

4.3.3 Prior anti-neoplastic therapy

Number and percentage of patients with prior anti-neoplastic medications/therapies (including medications for hematological disease, radiotherapy and SCT) will be summarized. Number of previous complete remissions, number of previous lines of therapies, setting of last medication (induction, consolidation, maintenance, salvage, conditioning for SCT), best response (including MRD status) of last medication and locations of last radiotherapy will also be summarized.

Prior anti-neoplastic medications for hematological disease will be summarized by anatomic therapeutic chemical (ATC) class, and preferred term.

Patients will also be classified and summarized by their response status at study entry:

- Primary refractory: If patient never had a morphologic CR prior to the study

- Chemorefractory: If patient had no CR to further lines of therapy after relapse from 1st line therapy
- Relapsed disease: If patient had a CR from other therapy and relapsed prior to the study, and does not qualify for chemorefractory

All prior anti-neoplastic medications, radiotherapy and SCT will be listed. The number of previous complete remissions and number of previous lines of therapies will also be listed.

4.3.4 Cytogenetic abnormalities

Number and percentage of patients with cytogenetic abnormalities (yes/no) and those with complex karyotypes (≥5 unrelated abnormalities) at study entry will be summarized. All cytogenetic abnormalities will be listed.

4.3.5 Others

All other data collected at baseline will be listed.

4.4 Protocol deviation summaries

The number and percentage of patients in the Full Analysis Set with any protocol deviation will be tabulated by the deviation category. Major protocol deviations leading to exclusion from the PPS will be summarized.

All protocol deviations will be listed.

4.5 Treatments (study treatment, rescue medication, other concomitant therapies, compliance)

The total cells infused (both cells and cells/kg) and total transduced CTL019 cells infused (both cells and cells/kg) will be listed and summarized using descriptive statistics. Weight provided to the manufacturing facility for CTL019 product manufacturing is used in calculating the weight adjusted doses.

Patients will be categorized as below, within or above the prescribed dose range. Patients with dose interruptions, as recorded in the dosage administration record eCRF, will be listed. Because the study drug of CTL019 is administered via one time infusion, no specific compliance will be summarized other than the CTL019 dose administration.

Prior and concomitant medications and significant non-drug therapies prior to and after the start of infusion will be listed by patient and summarized by ATC class and preferred term.

Antineoplastic therapies, including the lymphodepleting chemotherapies, received after enrollment but prior to infusion will be listed. Patients will also be summarized by the types of lymphodepleting chemotherapies received (i.e. fludarabine based lymphodepleting therapy, non-fludarabine based lymphodepleting therapy and no lymhodepleting therapy).

Transfusions collected per protocol requirement during the study will be listed.

Anti-cytokine medications are given for severe CRS due to CTL019 cells. Number of patients requiring anti-cytokine medications for the management of CRS will be summarized. The frequency and dose of rescue medications will also be summarized by preferred term.

4.6 Efficacy evaluation

4.6.1 Primary efficacy endpoint

The primary objective of the study is to evaluate the efficacy of CTL019 therapy as measured by overall remission rate (ORR) during the 3 months after CTL019 administration, which includes CR and CRi in the FAS.

The primary analysis will be based on the IRC assessment.

In addition, sensitivity analysis will be performed using the local investigator's response assessment instead of the IRC's assessment.

4.6.1.1 Variable

The primary endpoint is the ORR during the 3 months after CTL019 administration as determined by IRC assessment. The ORR is defined as the proportion of patients with a best overall disease response of CR or CRi. The best overall disease response is the best disease response recorded from first CTL019 infusion until start of new anticancer therapy (including SCT).

Best overall response will be assigned according to the following order:

1. CR
2. CRi
3. No response
4. Unknown

The best overall disease response for a patient is always calculated, based on the sequence of overall disease responses.

For the best overall disease response to be categorized as CR or CRi, there must be no clinical evidence of relapse as assessed by peripheral blood and extramedullary disease assessment (physical exam and CNS symptom assessment) at a minimum of 4 weeks (28 days) after the initial achievement of CR or CRi. Please note, if additional assessments of bone marrow and/or CSF are performed in the same evaluation, they will also need to show remission status (Section 3.4.2).

If a patient achieved CR or CRi once, without maintaining for at least 28 days, the best overall response for this patient will be considered as 'No response'. If a patient achieved CR or CRi once, but did not perform any subsequent response assessment, the best overall response for this patient will be considered as 'Unknown'.

See also the Section 3.4 for details regarding the definition of overall disease response.

4.6.1.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis will be performed by testing whether the ORR within 3 months is greater than 20% at overall one-sided 2.5% level of significance, i.e.,

$$H_0: p \leq 0.2 \text{ vs. } H_a: p > 0.2.$$

The primary efficacy endpoint, ORR within 3 months, will be analyzed at the interim look and final look following a group sequential design. The ORR will be summarized along with the 2-sided exact Clopper-Pearson confidence intervals (CI) with coverage level determined by the O'Brien-Fleming type α-spending approach according to Lan-DeMets as implemented in East 6.3 (Lan and DeMets, 1983). The study will be considered successful if the lower bound of the 2-sided exact confidence interval for ORR is greater than 20%, so that the null hypothesis that the ORR is less than or equal to 20% can be rejected.

The primary efficacy endpoint, ORR will be analyzed based on the data observed in the IEAS and FAS at interim and final analysis respectively.

In addition, time to response (CR or CRi) will also be summarized descriptively for responders.

4.6.1.3 Handling of missing values/censoring/discontinuations

Patients in the study who are of unknown clinical response will be treated as non-responders.

In case of missing data for the full evaluation required to qualify for a certain response category, the overall evaluation "unknown" will be assigned unless at least one observation was made which qualifies for relapse. Relapse can be determined by the relapsed component alone.

Other missing data are simply noted as missing on appropriate tables/listings.

The censoring rules for time to event endpoints are specified in the corresponding sections in Section 4.6.3.

4.6.1.4 Supportive analyses

The analysis of the primary endpoint will be performed among all patients in the PPS using the same methodology as outlined at interim and final analysis, respectively.

The analysis of primary endpoint will also be performed among all patients in the IEAS or FAS (at interim and final analysis respectively) plus enrolled patients who have discontinued prior to CTL019 infusion.

In addition, the analysis of the primary endpoint will also be performed using all patients in the IEAS or FAS (at interim and final analysis respectively) plus those who satisfy all clinical eligibility criteria and have discontinued prior to CTL019 infusion.

Proportion of patients attaining CR or CRi at Day 28 +/- 4 days post CTL019 infusion, among all patients in the IEAS or FAS (at time of interim and final analysis respectively), will be summarized along with exact 95 % CI.

4.6.2 Key secondary efficacy endpoint

4.6.2.1 ORR within 3 months in all patients infused with CTL019 from US manufacturing facility

The first key secondary objective of the study is to evaluate the efficacy of CTL019 therapy from US manufacturing facilities as measured by overall remission rate (ORR) during the 3 months after CTL019 administration by IRC assessment among patients who receive CTL019

therapy from US manufacturing facility in IEAS and FAS at interim and final analysis respectively.

The hypothesis testing will be performed to test whether the ORR within 3 months is less than or equal to 20% against the alternative hypothesis that ORR is greater than 20%.

This hypothesis testing will only be performed when the primary objective is met, so that the family-wise type I error rate will be controlled at one-sided 2.5% level under this hierarchical testing scheme. The type I error probability will be controlled by using a Lan-DeMets (O'Brien-Fleming) alpha spending function at 2.5% level of significance.

This key secondary endpoint will be summarized along with the 2-sided exact Clopper-Pearson confidence intervals with coverage level according to the above alpha spending function. This key secondary objective will be considered successfully met if the lower bound of the 2-sided exact confidence interval is greater than 20%, so that the null hypothesis above can be rejected.

4.6.2.2 Remission with MRD negative bone marrow in patients infused with CTL019 from all manufacturing facilities

The second key secondary objective of the study is to evaluate the percentage of patients who receive CTL019 from all manufacturing facilities and achieve a BOR of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry during the 3 months after CTL019 administration. The main analysis of this key secondary objective will be performed among all patients in the IEAS and FAS population at time of interim and final analysis respectively. See Protocol Appendix 1 for details of determination of MRD negativity.

The key secondary efficacy analysis will be performed by testing whether the percentage of MRD negative responder among all patients in IEAS or FAS as defined above is less than or equal to 15% against the alternative hypothesis that it is greater than 15% at overall one-sided 2.5% level of significance, i.e.,

$$H_0: p \leq 0.15 \text{ vs. } H_a: p > 0.15.$$

This hypothesis testing will only be performed when both the primary endpoint and the first key secondary endpoint are met, so that the family-wise type I error rate will be controlled at one-sided 2.5% level under this hierarchical testing scheme. The type I error probability will be controlled by using a Lan-DeMets (O'Brien-Fleming) alpha spending function at 2.5 % level of significance.

This key secondary endpoint will be summarized along with the 2-sided exact Clopper-Pearson confidence intervals with coverage level according to the above alpha spending function. This key secondary objective will be considered successfully met if the lower bound of the 2-sided exact confidence interval is greater than 15%, so that the null hypothesis above can be rejected.

The key secondary endpoint will also be summarized among those who achieve a BOR of CR or CRi during the 3 months after CTL019 administration.

Additional analysis will be done using the qPCR MRD analysis instead of flow cytometry.

The quality of response (i.e. proportion of patients with MRD negative disease response) at day 28 +/- 4 days after treatment using central assessment by flow cytometry will also be summarized. For patients who proceed to SCT in remission, the MRD status before SCT by

local assessment (flow or PCR) will be listed. Both quantitative MRD result and qualitative results (positive/negative) will be analyzed if available.

4.6.2.3 Remission with MRD negative bone marrow in patients infused with CTL019 from US manufacturing facility

The third key secondary objective of the study is to evaluate the percentage of patients who achieve a BOR of CR or CRi with a MRD negative bone marrow by central analysis using flow cytometry during the 3 months after CTL019 administration among all patients who receive CTL019 from US manufacturing facility.

The hypothesis testing will be performed to test whether the above rate is less than or equal to 15% against the alternative hypothesis that it is greater than 15%.

This hypothesis testing will only be performed when both the primary objective and the first two secondary endpoints are met, so that the family-wise type I error rate will be controlled at one-sided 2.5% level under this hierarchical testing scheme. The type I error probability will be controlled by using a Lan-DeMets (O'Brien-Fleming) alpha spending function at 2.5% level of significance.

This key secondary endpoint will be summarized along with the 2-sided exact Clopper-Pearson confidence intervals with coverage level according to the above alpha spending function. This key secondary objective will be considered successfully met if the lower bound of the 2-sided exact confidence interval is greater than 15%, so that the null hypothesis above can be rejected.

4.6.3 Other secondary efficacy endpoints

No formal hypothesis testing is planned other than for the primary objective and key secondary objectives. The other secondary efficacy objectives are outlined in the following sections. IRC assessment will be used in the main analysis of secondary endpoints that involve disease response. Note that IRC assessment is only performed during treatment and primary follow-up phase. Additional relapse information is collected for patients entering secondary follow-up in remission. The relapse information collected during secondary follow-up will be used in all time to event analysis that involves disease response assessment.

4.6.3.1 Percentage of patients who achieve CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment

This analysis will be conducted when all patients have completed 6 months post CTL019 infusion or have discontinued earlier, and hence will not be conducted at the interim analysis.

The percentage of patients who are in CR or CRi at Month 6 without SCT (post CTL019 infusion) between CTL019 infusion and Month 6 response assessment, among all patients in FAS, will be summarized with exact 95% CI. In addition, the percentage will also be summarized among all patients who achieved CR or CRi.

The patient will be considered to be in CR or CRi at Month 6 if there is at least one CR or CRi assessment after day 167 (i.e. >30.4375 × 5.5) without any relapse prior to this CR or CRi assessment. If such patient does not have SCT prior to Month 6, this patient is considered as

having achieved CR or CRi at Month 6 without SCT between CTL019 infusion and Month 6 response assessment.

Here the time of proceeding to SCT is defined as the time of commencing the conditioning regimen as required for hematopoietic SCT. This definition applies to all analyses involving SCT.

4.6.3.2 Percentage of patients who achieve CR or CRi and then proceed to SCT while in remission before Month 6 response assessment

This analysis will be conducted when all patients have completed 6 months post CTL019 infusion or have discontinued earlier, and hence will not be conducted at the interim analysis.

The percentage of patients who achieve CR or CRi and then proceed to SCT during remission before Month 6 response assessment, among all patients in FAS will be summarized with exact 95% CI. In addition, the percentage will also be summarized among all patients who achieved CR or CRi. All patients that proceed to SCT post CTL019 infusion will be listed.

For patients who discontinue and undergo SCT before the scheduled Month 6 evaluation, they will be considered to have met this secondary endpoint if the patients are still in morphologic remission, i.e. the DOR is not lost or censored.

The "Month 6" evaluation is as defined in Section 4.6.3.1.

4.6.3.3 Duration of remission (DOR)

Duration of remission is defined as the duration from the date when the response criteria of CR or CRi is first met to the date of relapse or death due to underlying cancer.

In the main analysis of DOR (Method 1), in case a patient does not have relapse or death due to underlying cancer prior to data cutoff, DOR will be censored at the date of the last adequate disease assessment on or prior to the earliest censoring event (except for SCT). The censoring reason could be

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy (also see below for handling SCT)
- Adequate assessment no longer available
- Event after at least two missing scheduled disease assessments

In addition, if there are any patients who respond to CTL019 but experience death due to any reason other than ALL, death due to reason other than ALL will be considered as a competing risk event to other events of interest (relapse or death due to ALL). Sensitivity analyses will be performed in which death due to reason other than ALL will be censored.

As SCT may be a further treatment option in responding patients, it is appropriate to consider the date of SCT as censoring date, instead of censoring at the last disease assessment date.

A sensitivity analysis will be performed in which the date of relapse or death (if due to the underlying cancer) after SCT will be used for the calculation of DOR as a sensitivity analysis.

If a patient receives SCT after a CR or CRi, relapse or survival status after SCT will be recorded on the corresponding follow-up eCRFs, although data on individual disease response components (e.g. bone marrow) will not be collected. Censoring due to SCT (Method 1) will overestimate the rate of relapse and therefore may be considered inappropriate for the main analysis when a substantial number of patients choose to receive SCT (CHMP 2010). Therefore the above described sensitivity analysis will be performed if there is at least 1 patient with SCT after CTL019 infusion while in remission.

The proposed analyses for DOR are summarized in Table 4-1 below.

Table 4-1 Analyses of duration of remission

	Death due to reason other than underlying cancer	SCT after remission
Method 1	Competing risk analysis	Censor at time of SCT
Method 2	Censor at last adequate disease assessment	Censor at time of SCT
Method 3	Competing risk analysis	Ignore SCT
Method 4	Censor at last adequate disease assessment	Ignore SCT

DOR will be assessed only in patients with the best overall response of CR or CRi. The estimated percentage of relapsed patients (at 6 months, 12 months, etc.) will be presented with 95% confidence intervals using the cumulative incidence function (CIF) or the Kaplan-Meier (KM) method.

For Method 1 and Method 3, the CIF is used to estimate the probability of the event of interest in the presence of the competing risks (Kim 2007). These analyses will only be performed if there is at least 1 patient with competing risk event.

For Method 2 and Method 4, the distribution function of DOR will be estimated using the KM method. The median DOR along with 95% confidence intervals will be presented if appropriate.

If a considerable number of patients receive SCT while in remission after CTL019 infusion, then exploratory analyses may be performed on patients who achieve CR/CRi after CTL019 infusion to assess the effect of SCT on DOR. Baseline disease characteristics and post-baseline factors (e.g. time to CR/CRi, minimal residual disease) that may be correlated with the decision to receive SCT and with DOR will be identified. A Cox model with SCT as a time dependent covariate and potential confounding factors as additional covariates may then be explored in patients who achieve CR/CRi after CTL019 infusion. The hazard ratio (SCT v/s No SCT after CR/CRi) estimate along with its 95% confidence interval will be provided. Additional exploratory analyses may be considered to account for the confounding factors.

For relapse patients, the following characteristics of the initial relapse will be summarized:

- Site of initial relapse:
  - Bone marrow or peripheral blood relapse
    - With extramedullary relapse
    - Without extramedullary relapse
    - Unknown extramedullary status
  - Extramedullary only relapse

- CD19 status of initial bone marrow or peripheral blood relapse: Determined by ALL phenotyping from bone marrow or peripheral blood flow cytometry assessment:
  - CD19 positive
  - CD19 dim
  - CD19 negative
  - CD19 positive/negative
  - Unknown

If CD19 status is obtained from both bone marrow and peripheral blood, the bone marrow result will be used.

4.6.3.4 Relapse free survival (RFS)

Relapse free survival is measured by the time from achievement of CR or CRi whatever occurs first to relapse or death due to any cause during CR or CRi.

In case a patient does not have relapse or death due to any cause prior to data cutoff, RFS will be censored at the date of the last adequate disease assessment on or prior to the earliest censoring event (except for SCT). The censoring reason could be

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy (see below for handling SCT)
- Adequate assessment no longer available
- Event after at least two missing scheduled disease assessments

In the main analysis of RFS, patients who proceed to SCT after CTL019 infusion will be censored at the time of SCT (see Section 4.6.3.3 for the rationale). In addition, a sensitivity analysis of RFS will be performed without censoring SCT, if there is at least 1 patient with SCT after CTL019 infusion while in remission.

RFS will be assessed only in patients with the best overall response of CR or CRi. The distribution function of RFS will be estimated using the KM method. The median RFS along with 95% confidence intervals will be presented if appropriate.

4.6.3.5 Event free survival (EFS)

Event free survival is the time from date of first CTL019 infusion to the earliest of the following:

- Death from any cause after remission
- Relapse
- Treatment failure: Defined as no response in the study and discontinuation from the study due to any of the following reasons:
  - Death
  - Adverse event

- Lack of efficacy
- New anticancer therapy

In case of treatment failure, the event date will be set to study Day 1 (CHMP 2010). In addition, a sensitivity of EFS will be performed by considering time of discontinuation from the study as the event time for treatment failure, instead of setting to study Day 1.

In case a patient does not have relapse, death due to any cause or treatment failure (e.g. discontinuation as a result of withdrawal of consent, lost to follow-up, protocol violation or administrative problems) prior to data cutoff, EFS is censored at the last adequate disease assessment date on or prior to the earliest censoring event (except for SCT). The censoring reason could be

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy (see below for handling SCT)
- Adequate assessment no longer available
- Event after at least two missing scheduled disease assessments

In the main analysis of EFS, patients who proceed to SCT while in remission after CTL019 infusion will be censored at the time of SCT (see Section 4.6.3.3 for the rationale). In addition, a sensitivity analysis of EFS will be performed without censoring SCT, if there is at least 1 patient with SCT after CTL019 infusion while in remission.

EFS will be assessed in all patients (IEAS and FAS). The distribution function of EFS will be estimated using the KM method. The median EFS along with 95% confidence intervals will be presented if appropriate.

4.6.3.6 Overall survival (OS)

Overall survival is the time from date of first CTL019 infusion to the date of death due to any reason.

Patients not known to have died at the data cut-off date are censored at their last contact date, which is defined as the latest date they were known to be alive. No censoring will be done in case of SCT. Thus, patients should be followed-up for survival also in case of SCT.

OS will be assessed in all patients (IEAS and FAS). The distribution function of OS will be estimated using the KM method. The median OS along with 95% confidence intervals will be presented if appropriate.

4.6.3.7 Efficacy in patients infused with CTL019 manufactured by [redacted]

The ORR and MRD negative remission rate will be summarized with 95% exact confidence intervals for patients infused with CTL019 manufactured by [redacted].

This analysis is not applicable at interim analysis because there is no patient infused with CTL019 from [redacted] at time of interim analysis.

4.7 Safety evaluation

4.7.1 Analysis set and reporting periods for the analyses

Table 4-2 summarizes the mutually exclusive safety reporting periods as well as the patients to be included in each of the segments. Note that the post-infusion period will be the main period of safety reporting (see Section 4.7.2 for details).

Table 4-2 Safety reporting periods

Period	Definition	Patients to be included
Pre-treatment period	From day of patient's informed consent to the day before first lymphodepleting chemotherapy dose or the pre-infusion visit if the lymphodepleting chemotherapy is not given	Screened patients
Lymphodepleting period (note: this period only applies to patients who received lymphodepleting chemotherapy)	From the first day of lymphodepleting chemotherapy • to the day before infusion of CTL019, for patients who received infusion, or • to the earlier of date of discontinuation and 30 days after last dose of lymphodepleting chemotherapy for patients who didn't receive infusion of CTL019	All patients who received lymphodepleting chemotherapy
Post-infusion period	Starting at day of first CTL019 infusion until end of study (60 months from CTL019 infusion)	Safety Set

4.7.2 Adverse events

The adverse events reporting follows a modified safety reporting rule as described in Protocol Appendix 3.

Reporting of AEs (except for CRS and graft versus host disease (GVHD)) will be based on MedDRA (latest version per database lock) and Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The grading of CRS and GVHD will be based on protocol specific grading scales (Protocol section 6.2.4.2, Table 6-1 and Table 6-3, respectively).

Summary tables for AEs will be provided for AEs that started or worsened during the post-infusion period, i.e. the ***CTL019-treatment-emergent*** AEs. However, all safety data (including all observation periods as defined in Section 4.7.1) will be listed and with the period (as defined in Section 4.7.1) flagged for the starting date of the AE.

The incidence of CTL019-treatment-emergent AEs (new or worsening during the post-infusion period) will be summarized by system organ class, preferred term, severity (based on CTCAE grades), and relation to study drug. A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event. The frequency of CTC grade 3 and 4 AEs will be summarized separately.

4.7.2.1 Adverse events of special interest (AESI)

AESIs are defined by the search criteria form in the following location in CREDI:

/CREDI Projects/C/CTL019A/Integrated Medical Safety/

The risks and search criteria defined therein will be updated on a regular basis at CTL019 program level. The most recent version of the search criteria form will be used for the reporting activity.

The following risks are regarded as AESI:

- Cytokine release syndrome
- Tumor Lysis Syndrome
- Febrile neutropenia
- Infection
- Transient neuropsychiatric events (events within 8 weeks of infusion)
- Hematopoietic cytopenias not resolved by day 28

AESI that occur within 8 weeks of the last CTL019 infusion will be summarized by group term and preferred term.

For hematopoietic cytopenias not resolved by day 28, analysis on laboratory results will also be performed (Section 4.7.3) in addition to the adverse events as reported by the investigator. Infections started on or after day 28 among patients with grade 3 or 4 neutropenia not resolved by day 28 per lab results will be listed.

4.7.2.2 Summaries of adverse events

Post-infusion period:

The following AE summaries will be produced for the Safety Set:

- Adverse events, regardless of study drug relationship, by primary system organ class, preferred term and maximum grade
- Adverse events, suspected to be study drug related, by primary system organ class, preferred term and maximum grade
- Deaths post infusion, by primary system organ class and preferred term
- Serious adverse events, regardless of study drug relationship, by primary system organ class and preferred term and maximum grade
- Serious adverse events, suspected to be study drug related, by primary system organ class and preferred term and maximum grade
- Adverse events of special interest, regardless of study drug relationship, by group term, preferred term and maximum grade
- Adverse events of special interest, suspected to be study drug related, by group term, preferred term and maximum grade
- Adverse events leading to study discontinuation, regardless of study drug relationship, by primary system organ class and preferred term
- Non-Serious Adverse events, regardless of study drug relationship, by primary system organ class and preferred term
- Bleeding and cardiac events, regardless of study drug relationship, by group term, preferred term, and maximum grade

The search criteria for bleeding and cardiac events are defined by the search criteria form in the same location as the AESI above (Section 4.7.2.1).

Lymphodepleting period:

In addition, AEs that started or worsened during the lymphodepleting period will be summarized for all patients in the Enrolled Set who received lymphodepleting chemotherapy. The following tables will be produced:

- Adverse events, regardless of study treatment relationship by primary system organ class and preferred term
- Serious adverse events, regardless of study treatment relationship by primary system organ class and preferred term
- Adverse events, with suspected study treatment relationship by primary system organ class and preferred term
- Serious adverse events, with suspected study treatment relationship by primary system organ class and preferred term

Pre-treatment period:

AEs that started or worsened during the pre-treatment period will be separately summarized for the Enrolled Set:

- Adverse events, by primary system organ class, preferred term and maximum grade
- Serious adverse events, by primary system organ class and preferred term

4.7.2.3 Safety in patients infused with CTL019 manufactured by [redacted]

Key safety summaries for adverse events regardless of relationship to study drug by System Organ Class (SOC) and PT, and adverse events of special interest will be performed on the Safety Set.

4.7.3 Laboratory abnormalities

For laboratory tests covered by the CTCAE, the study's biostatistics and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following summaries will be generated separately for hematology and biochemistry laboratory tests for Safety Set:

- Shift tables using CTCAE grades to compare baseline to the worst post-infusion value.
    - for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)
- Change from baseline to the worst post-infusion value, with descriptive statistics of baseline value, worst post-infusion value and the change.

The shift tables will be generated by timing: Within 8 weeks post CTL019 infusion, >8 weeks to 1 year post CTL019 infusion, >1 year post CTL019 infusion.

In addition, percentage of patient with Grade 3 or 4 hematopoietic cytopenias 28 days post CTL019 infusion will be summarized. Among patients with Grade 3 or 4 hematopoietic cytopenias 28 days post CTL019 infusion, the timing of resolution to Grade 2 or below will be summarized via Kaplan-Maier method. Grading of cytopenias will be derived using lab results in absolute lymphocytes (hypo), absolute neutrophils (hypo), hemoglobin (hypo), platelet count (hypo) or WBC (hypo) according to CTCAE 4.03. If a patient did not achieve resolution at the last lab assessment, timing of resolution will be censored at the last assessment. The median time to resolution and KM estimates of % unresolved cases at different time point (month 2, month 3 and etc.) will be summarized.

The following listings will be provided for Enrolled Set.

- Listing of patients with laboratory abnormalities of CTC grade 3 or 4 with the corresponding CTC grades and the classifications relative to the laboratory reference ranges.
- Listing of all laboratory data with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges.

4.7.4 Immunogenicity

Interpretation of immunogenicity anti-CTL019 assay will be summarized and listed for Safety set.

4.7.5 Cytokine release syndrome and anti-cytokine therapies

To explore the relationship between CRS and other endpoints, the goal of this statistical analysis should be considered as the generation of new scientific hypotheses and observing new trends, since the studies are not adequately powered to propose a scoring system.

Clinical and biomarker data will be analyzed to potentially identify an early predictive score which reflects the risk of developing severe cytokine release syndrome. Only parameters that can be potentially utilized in clinical setting by treating physicians will be considered for the score development.

Detailed information regarding the CRS will be summarized by day 28 disease response from IRC assessment. Information summarized includes: maximum CRS grade, time to onset of CRS; duration of CRS; time to Grade 3/4 CRS, concurrent infections, timing and duration of ICU stay, selected complications, and use of anti-cytokine therapies, etc.

In addition, time to first CRS onset will be summarized for all patients using the Kaplan-Meier (KM) method. For those patients without CRS, time to first onset will be censored. The censoring date is the minimum of the cut-off date, end of study evaluation (i.e., completion of the last phase of the study) and date of death (if applicable). Time to resolution of the first CRS will also be summarized using KM method for patients with CRS. In case the end date of a CRS is missing, it will be censored / imputed as the minimum of the following dates: the cut-off date, end of study evaluation (i.e., completion of the last phase of the study), date of death (if applicable).

Peak cytokine level, time to high fever onset, CTL019 PK parameters (e.g. Cmax and AUC0-d28), baseline tumor burden, CTL019 product characteristics (i.e. CD3+CD45+ [%], transduction efficiency [%], vector DNA sequence for CTL019 PCR [copies/cell]) and CTL019 dose administered will be plotted against the maximum CRS grade using strip plot as appropriate. The relationship between maximum CRS grade of the overall study vs CTL019 dose will also be explored using strip plots.

Individual patient time-profile for key inflammatory markers and cytokine parameters up to month 1 will be plotted, with annotation of tocilizumab and siltuximab usage.

4.7.6 Growth data

For patients under 18 years of age at the time of CTL019 infusion, height and weight will be summarized at semi-annual intervals before and after starting CTL019, using the standard deviation score (SDS), velocity and velocity SDS. The relevant height and weight values for each semi-annual period are defined using time windows, as defined in Section 5.4.

SDS is calculated using the formulae (provided by Centers for Disease Control and Prevention (CDC)):

$$\text{SDS} = \frac{\left(\frac{X}{M}\right)^{L} - 1}{LS} \text{ if } L \neq 0, \qquad \text{or} \qquad \text{SDS} = \frac{log\left(\frac{X}{M}\right)}{S} \text{ if } L = 0,$$

where X is height in centimeters or weight in kilograms, and L, M and S are height-, weight-, sex- and age-specific reference values from the CDC Growth Charts (http://www.cdc.gov/growthcharts/percentile_data_files.htm). The files for height and weight are named STATAGE and WTAGE for children older than 2 years (see Appendix). Age is listed at the half month point for the entire month; for example, 1.5 months represents 1.0 month up to but not including 2.0 months of age. SDS is actually a Z score that measures the distance from the population mean in units of standard deviations. That is, SDS < 0 refers to values lower than the population mean, and for example SDS ≤ -1.645 refers to values in the lowest 5%. (The usual percentile more commonly used in the clinical practice can be derived from the Z-score by a normal distribution).

Height velocity is defined as follows:

Height velocity (cm/6-months) = (height in time window *k* – height in time window *k-1*)

÷ ([assessment date in time window *k* – assessment date in time window *k-1*] ÷ [365.25/2]),

and similarly for weight velocity.

Velocity SDS is calculated as (velocity – mean) / SD, where mean and SD are obtained as the height-, weight-, sex- and age-specific values in Tables 5 to 8 in Baumgartner (1986), where the age category immediately above the patient's exact age (at the assessment date in time window *k*) should be used. Velocity SDS will only be calculated for time window *k* if data also exists for time window *k-1*, since calculating across multiple units of 6 months requires more than one reference value to be taken into account.

Height/weight SDS and velocity SDS will be summarized using descriptive statistics (mean, standard deviation, range) for each time window, as well as by presenting number of patients with SDS values lower/higher than 5^{th}/95^{th} percentiles respectively. Box plots will also be

plotted for each time window. All height/weight SDS, velocity and velocity SDS data will be listed, and values of SDS and velocity SDS outside of the central 95% of population values will be flagged as either High (SDS $\geq$ 1.645) or Low (SDS $\leq$ -1.645).

Depending on the actual enrolled population (e.g. country, race, etc.), adjustment of the method may be made if appropriate.

4.7.7 Puberty Stage

Puberty stage will only be analyzed among pre-pubescent patients, i.e., using patients from the Safety Set who were classified as Tanner Stage 4 or lower at the latest assessment prior to the infusion of CTL019.

Tanner Stage includes two components for boys, namely testis and pubic hair, and two components for girls: breast development and pubic hair. It is expected that data will become available during the trial on a proportion of patients as they go through puberty attaining higher levels of the Tanner Stage. For the age at which Tanner Stages 2-5 are achieved, age at thelarche (females), age at menarche (females) and age at adrenarche (males), summary statistics from Kaplan-Meier distributions will be determined, including the median age and the proportions of patients reaching these milestones at some given ages. The statistics will be given as point estimates with 95% confidence intervals.

Delayed puberty in girls is defined as failure to attain Tanner Stage 2 (for both breast development and pubic hair) by age 13, or absence of menarche by age 15 or within 5 years of attainment of Tanner Stage 2 (Fenichel et al. 2012). Delayed puberty in boys is defined as failure to attain Tanner Stage 2 (for both testis and pubic hair) by age 14 (Crowley et al. 2012). Rates of delayed puberty will be presented for boys and girls separately, along with 95% confidence intervals, among the patients who did not have delayed puberty at baseline.

4.7.8 Other safety data

Vital signs will be collected as clinically needed. Findings supportive of GVHD will be listed for patients who have received prior allogeneic SCT.

Karnofsky/Lansky performance scores will be listed by subject.

4.8 Pharmacokinetic analysis

PAS will be used for all PK summaries (tables and figures). FAS will be used for PK data listings.

CTL019 concentrations in peripheral blood and bone marrow (and CSF if available) will be listed, graphed, and summarized by time point as assessed by the following:

- CTL019 transgene levels as measured by q-PCR
- CTL019 transduced cells measured by flow cytometry of CD3-positive, CD3-positive/ CD4-positive and CD3-positive/CD8-positive CTL019 transduced cells.

The PK parameters listed in Table 4-3 will be estimated from the individual concentration versus time profiles using a non-compartmental approach within Phoenix® (Pharsight, Mountain View, CA). The non-quantifiable concentrations will be imputed to zero for PK

concentration summaries, and will not be included for estimation of PK parameters. Results reported but deemed unreliable will be flagged and excluded from the summaries and PK parameter derivations.

Table 4-3 Noncompartmental pharmacokinetic parameters

Parameter	Definition
AUC 0 - Tmax	The AUC from time zero to Tmax in peripheral blood (% or copies/µg x days)
AUC Tmax - 28d and 84d	The AUC from time Tmax to day 28 and 84 or other disease assessment days, in peripheral blood (% or copies/µg x days)
AUC 0 - 28d and 84d	The AUC from time zero to day 28 and 84 or other disease assessment days, in peripheral blood (% or copies/µg x days)
Cmax	The maximum (peak) observed in peripheral blood drug concentration after single dose administration (% or copies/µg)
Tmax	The time to reach maximum (peak) peripheral blood drug concentration after single dose administration (days)
T1/2	The half-life associated with the disposition phase slopes (alpha, beta, gamma etc.) of a semi logarithmic concentration-time curve (days) in peripheral blood
Clast	The last observed quantifiable concentration in peripheral blood (% or copies/ug)
Tlast	The time of last observed quantifiable concentration in peripheral blood (days)

Descriptive statistics of PK parameters (mean, standard deviation, coefficient of variation, geometric mean, CV% geometric mean, median, min and max) will be summarized by day 28 disease response from IRC assessment. When a geometric mean will be presented, it will be stated as such. A range of values will be presented for selected variables. For Tmax median values and ranges only will be given.

The relationship between anti-cytokine treatment, use of steroids, occurrence of immunogenicity or other relevant covariates and PK might be explored. Population and/or mechanistic PK / PD models may also be generated.

For patients who were treated with tocilizumab during CRS, the tocilizumab concentrations will be summarized by time points (depending upon sample availability) relative to time of first tocilizumab dose.

CTL019 PK parameters will be summarized by tocilizumab usage to investigate the effect of tocilizumab on CTL019 PK.

4.8.1 CTL019 PK in patients infused with CTL019 manufactured by [redacted]

The CTL019 PK parameters for CTL019 transgene levels as measured by q-PCR will also be summarized. The CTL019 PK parameters as measured by flow cytometry (exploratory only) will also be summarized, as appropriate.

4.9 Biomarkers analyses

As a project standard, Novartis Oncology BDM will analyze only biomarkers collected in the clinical database. For exploratory markers, since the studies are not adequately powered to

assess specific biomarker–related hypotheses, the goal of these exploratory statistical analyses should be considered as the generation of new scientific hypotheses. These hypotheses may be compared with results found in literature as well as verified with data derived from subsequent clinical trials. No adjustment for multiple comparisons is usually planned for exploratory analyses. Furthermore, additional post hoc exploratory assessments are expected and may be performed.

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue the analysis of blood / archival tumor samples / fresh tumor biopsies / fine needle aspirates due to either practical or strategic reasons (e.g. issues related to the quality and/or quantity of the samples or issues related to the assay). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

The analyses to be performed for the CSR are outlined below. Additional analyses that may be performed after the completion of the end-of-study CSR will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in a stand-alone analysis plan document, as appropriate.

4.9.1 Biomarker Data Analysis Set

The FAS will be used for all biomarker analysis. Assessment of associations between biomarker and safety data will be conducted using the Safety Set.

4.9.1.1 Data Handling of Serum Cytokine Data

Serum cytokine data represent quantitative soluble protein measurements that tend to follow a log normal distribution. Thus, a log10 transformation of the data is typically required for normalization prior to performing any statistical modeling. Values below the lower limit of quantitation (which may be reported with the label “LLOQ” or have a numerical value below the assay’s lower limit of quantification) will be imputed / replaced as 0.5×LLOQ, which will be specified by the performing lab and is assay and analyte specific. In some cases a value, although below LLOQ, is reported, this value should not be used and the data should be imputed as 0.5×LLOQ.

For values above the upper limit of quantification (either reported as “ULOQ” or a numerical value greater than the assays upper limit of quantification), the values will be set to the ULOQ threshold of the assay.

4.9.2 Basic Tables, Listings and Figures

4.9.2.1 B-cell and T-cell level

The levels (%) of CD19+ total B cells amongst viable WBC in peripheral blood will be summarized by day 28 response of IRC assessment and time point (see Section 5.4). The levels (%) of T cells amongst mono-nuclear cells (lymphocytes and monocytes with the exclusion of granulocytes) in peripheral blood and bone marrow will be described.

CD19 phenotype determined by bone marrow flow cytometry assessment (CD19 positive, CD19 dim, CD19 negative, CD19 positive/negative, Unknown) and CD19+ intensity level among B-ALL cells in bone marrow at baseline and time of bone marrow or blood relapse will be summarized.

It is anticipated that all patients who achieve complete remission will exhibit B-cell aplasia. Time to B-cell recovery will be summarized. Here B cell recovery is defined as the time from onset of remission date to the earliest time when the percentage of CD19+ total B cell among viable WBC in blood is at least 1%. If no B cell recovery is observed, time to B cell recovery is censored at the last B cell result. Note that if CD19+ ALL tumor cells are also present in the blood (recurrence), total B cells are affected by the malignant B cells and hence should be interpreted with caution.

Data may also be summarized by response status and potentially graphed using strip plots. Patient level and average longitudinal plots of the cell counts and percent changes from baseline may be generated.

For abnormal T cell or B cell results, associated safety events such as infections and use of associated therapies (i.e. antibiotics, immunoglobulin replacement) will be investigated using patient listings.

4.9.2.2 Soluble immune factors

Soluble immune and inflammatory cytokines (e.g. IL-10, interferon gamma, IL-6, CRP, and Ferritin) will be listed and summarized by patient and time point. If both the baseline and post baseline values are below LLOQ, absolute, percent and fold change from baseline will not be imputed and reported as missing. Summaries of baseline and change from baseline (absolute change, percent change and fold change) at each time point will be summarized in tables that include sample size, mean, standard deviation, %CV, median, minimum and maximum. Optionally the number and percent of missing values or the values below LLOQ for each time point will be reported.

CRP and ferritin results assessed by local lab will be used for summary.

Baseline levels may also be summarized by clinical response status and severity of CRS and potentially graphed using strip plots. In addition, the maximum change from baseline measure for each cytokine may also be graphed against clinical response status and severity of CRS response using strip plots. Patient level and averaged cytokine measures and change from baseline may be displayed using longitudinal plots.

4.9.2.3 [redacted]

[redacted]

4.9.3 [redacted]

[redacted]

4.10 [redacted]

[redacted]

4.11 Patient reported outcome (PRO) and healthcare resource utilization

4.11.1.1 Patient reported outcome

Patient Reported Outcomes (PRO) will be assessed using PedsQL and EQ-5D. PedsQL™ and EQ-5D will be completed by patients aged 8 and above. Descriptive statistics (e.g. mean, median, and frequency) and change from baseline of the summary scores for each post baseline time-point/window of assessment will be provided based on all available data at the time of analysis. IEAS or FAS will be used for all analysis at interim and final analysis respectively.

No imputation will be applied if the total or subscale scores are missing at a visit.

Separate summaries will be provided for month 3 and 6 EQ-5D and PedsQL results for those patients who achieve best overall response CR/CRi.

Subgroup analysis by age group may be performed as ad hoc analysis if there is sufficient number of patients within each age subgroup.

4.11.1.1.1 EQ-5D

The EQ-5D health state is represented by the answer to the 5 dimensions of the questionnaire (mobility, self-care, usual activity, pain/discomfort, anxiety/depression in this order). Each question has 3 levels answers:

- level 1: no problems
- level 2: some problems
- level 3: a lot of problems

For each question, the level at baseline, as well as the change of level in each post baseline time-point/window of assessment will be summarized.

In addition, there is a general question about the overall health (EQ-VAS) with range 0-100 (the larger number indicates better health). The EQ-VAS values as well as the change from baseline will be summarized for each post baseline time-point/window of assessment.

4.11.1.1.2 PedsQL

The PedsQL questionnaire composes of 4 subscales: emotional, social, school and physical functioning scales. Each subscale contains 5-8 questions each with 5 choices indicating the frequencies. The items in each question will first be scored as the following: "Never"=100, "Almost Never"=75, "Sometimes"=50, "Often"=25, and "Almost Always"=0.

The mean scores in following categories will then be calculated:

- each of the 4 subscales (i.e. emotional, social, school and physical),
- the psychosocial health summary score (combining emotional, social and school functioning scales),
- the total score (combining all 4 subscales).

Descriptive statistics will be used to summarize the raw and change from baseline of the above summary scores for each post baseline time-point/window of assessment.

If more than 50% of the items are missing in a subscale for PedsQL, the score for this subscale will be considered missing for this assessment. Otherwise, the average of the non-missing items in the subscale will be used to impute for the missing items when calculate the score for the subscale.

4.11.1.2 Healthcare resource utilization

Data relating to resource utilization (described in Section 7.2.5 of study protocol) will be used to support health economic evaluations.

Number of CTL019 inpatients and outpatients infusions will be summarized. Descriptive statistics of hospitalizations, including the total and average number and duration of hospitalizations, timing and duration of ICU stay, etc., will be provided.

4.12 Subgroup analyses

4.12.1 Efficacy subgroup analyses

Subgroup analyses for ORR, MRD and DOR will be performed on the following based on the patient's baseline status:

- Age: <10 years, ≥10 years to <18 years, ≥18 years
- Gender: Male, Female
- Race: White, Asian, Other
- Ethnicity: Hispanic or Latino, Other
- Response status at study entry: Primary refractory, Chemorefractory, Relapsed disease

- Prior SCT therapy: Yes, No
- Eligibility for SCT: Eligible for SCT, ineligible for SCT
- Baseline bone marrow tumor burden: Low (defined as either morphologic or MRD result is <50% and neither is ≥50%), High (defined as either morphologic or MRD result is ≥50%)
- Baseline extramedullary disease presence: Yes, No
- Philadelphia chromosome/BCR-ABL: Positive, Negative
- Mixed-Lineage Leukemia (MLL) rearrangement: Yes, No
- Hypodiploidy: Yes, No
- BCR-ABL1-like: Yes, No
- Complex Karyotypes (≥5 unrelated abnormalities): Yes, No
- Down's syndrome: Yes, No

The rationale for performing subgroup analyses are as follows:

- Age, gender, race and ethnicity are demographic factors that are typically requested by health authorities to assess internal consistency of the study results and also have been shown to impact ALL outcome in first line and first relapse settings.
- Prior response status is a key prognosis factor due to potentially different rates of treatment related morbidity in patients who have relapsed following allogeneic SCT vs those who have not undergone SCT.
- Baseline bone marrow tumor burden and extramedullary disease presence are important indicators of overall disease burden, which is a potential predictive factor.
- BCR-ABL, MLL rearrangement, Hypodiploidy, BCR-ABL1-like gene signatures and complex karyotype (≥5 unrelated abnormalities) are high risk factors for ALL outcome in the first line and first relapse settings. Patients with these high risk factors have poorer diagnosis (Harrison et al 2010; van der Veer et al 2013; NCCN v6 2013). In case there are very few patients with these high risk features individually, analysis may be performed for patients with any of these high risk features versus those who do not.
- Patients with Down's syndrome are known to have increased ALL treatment related morbidity and mortality rates. Because of increased risk, stem cell transplant is often not recommended in this population. Therefore, the experience with CTL019 in this rare population may address an unmet medical need.

Subgroup analyses will only be performed if at least 5 patients are present in each subgroup. Some grouping of classes will be considered if there are too few patients in some subgroups.

Efficacy analyses in subgroups will generally be purely exploratory and are intended to explore the intrinsic consistency of any treatment effects found overall.

Subgroup analyses of the primary endpoint (ORR) will be performed on the FAS by presenting the point estimates in the subgroup with the exact 95% CIs. Summary tables and forest plots will be presented.

4.12.2 Safety subgroup analyses

Key safety summaries for adverse events regardless of relationship to study drug by SOC and PT, and adverse events of special interest will be repeated on the Safety Set in the following subgroups:

- Age: <10 years, ≥10 years to <18 years, ≥18 years
- Gender: Male, Female
- Race: White, Asian, Other
- Ethnicity: Hispanic or Latino, Other
- Response status at study entry: Primary refractory, Chemorefractory, Relapsed disease
- Prior SCT therapy: Yes, No
- Down's syndrome: Yes, No

Summary tables will only be performed if at least 5 patients are present in each subgroup. Some grouping of classes will be considered.

4.13 Determination of sample size

In a previous study of clofarabine in patients with r/r B-cell ALL who have had 2 or more prior regimens, the reported ORR was 20% (95% CI [10%, 34%]; Jeha et al. 2006). Hence, an ORR of 45% that excludes a 20% ORR at the 0.025 significance level would indicate meaningful efficacy in this highly refractory population.

The final analysis of the primary endpoint will be performed after all patients infused with CTL019 have completed 3 months follow-up from study day 1 infusion or discontinued earlier. The sample size for the final analysis of the primary endpoint will be up to 76 patients.

Based on the null hypothesis of ORR ≤ 20% and alternative hypothesis of ORR >20%, 76 patients in the FAS will provide more than 95% power to demonstrate statistical significance at one-sided cumulative 0.025 level of significance, if the underlying ORR is 45% and taking into account the interim analysis as described in Section 4.14. In this setting, an ORR of 23/76=30% will be needed to claim success.

Within the expected sample size of 76 patients with CTL019, at least 10 patients will be treated with CTL019 manufactured by the [redacted]. If there are at least 6 patients among them who achieved best overall response of CR or CRi, the lower bound of the 95% confidence interval will be higher than 20%. The probability of observing at least 6 CR or CRi among the 10 patients will be 26% if the true ORR is 45%, and will be 84% if the true ORR is 70%.

Table 4-4 Confidence intervals for ORR in patients infused with CTL019 manufactured by the [redacted]

Total number of patients	CR + CRi	95% Exact CI
10	5	(18.7%, 81.3%)
	6	(26.2%, 87.8%)
	7	(34.8%, 93.3%)
	8	(44.4%, 97.5%)
	9	(55.5%, 99.7%)

	10	(69.2%, 100%)

The actual number of patients to be enrolled will depend on the pre-infusion dropout rate. Limited data are available so far to provide robust estimate on the pre-infusion dropout rate. Assuming 20% to 25% enrolled patients will not be infused due to reasons such as manufactory failure, worsening of patient's condition, etc., approximately 95 patients are estimated to be enrolled to reach the number of patients required.

4.13.1 Power for analysis of key secondary variables

4.13.2 ORR within 3 months in patients infused with CTL019 from US manufacturing facility

The same efficacy is assumed for patients infused with CTL019 in US manufacturing facility vs other manufacturing facilities. Under this assumption and conditional on the statistical significance of the primary endpoint, the overall power of this endpoint will be greater than 95%, taking in account an interim analysis will be performed with first 50 patients, and then a final analysis will be performed with up to 66 patients infused with CTL019 from US manufacturing facility.

4.13.3 Remission with MRD negative bone marrow in patients who received CTL019 from all manufacturing facilities

In previous studies in the r/r ALL setting, 67% to 82% patients achieved MRD negative status among patients who achieved CR or CRi (Topp et al 2015, O'Brien et al 2012). Considering that an ORR of 45% that excludes 20% at the 0.025 significance level would indicate meaningful efficacy for ORR, 34% of patients achieving MRD negative bone marrow that excludes 15% at the 0.025 significance level would indicate meaningful efficacy (i.e. 75% among complete responders) for the key secondary objective.

Based on the above assumptions, conditional on the statistical significance of the primary endpoint and the first key secondary endpoint, and taking into account the interim analysis with first 50 patients as described above, 76 patients in the FAS will provide greater than 95% power to demonstrate statistical significance for the key secondary endpoint at one-sided 0.025 level of significance, if the underlying percentage of patients who achieve BOR or CR or CRi with MRD negative bone marrow is 34%.

4.13.4 Remission with MRD negative bone marrow in patients who received CTL019 from US manufacturing facility

The same efficacy is assumed for patients infused with CTL019 in US manufacturing facility vs other manufacturing facilities. Under this assumption and conditional on the statistical significance of the primary and first 2 key secondary endpoints, the power of this endpoint will be 94%, taking into account an interim analysis will be performed with first 50 patients, and then a final analysis will be performed with up to 66 patients with CTL019 from US manufacturing facility.

4.14 Interim analyses

4.14.1 Interim analysis for the primary endpoint

An interim analysis is planned when the first 50 patients infused have completed 3 months from study day 1 infusion or discontinued earlier. The interim analysis will be performed by testing the null hypothesis of ORR within 3 months being less than or equal to 20% against the alternative hypothesis of ORR within 3 months being greater than 20% at overall one-sided 2.5% level of significance.

The study will not be stopped for outstanding efficacy at the interim analysis regardless of the interim result.

An α-spending function according to Lan-DeMets (O'Brien-Fleming), as implemented in East 6.3, will be used to construct the efficacy stopping boundaries (Lan and DeMets 1983). Based on the choice of α-spending functions described above, if the interim analysis is performed exactly with 50 patients and final analysis will include up to 76 patients (i.e. 50/76=65.8% information fraction), the lower bound of the 2-sided 98.9% exact CI of the ORR will need to be greater than 20% to declare statistical significance. As a result, an ORR of 19/50 = 38% is needed to claim success at interim. If the interim efficacy boundary is not crossed, 2-sided 95.4% exact CI will be used at final analysis correspondingly. As a result, an ORR of 23/76 = 30% will be needed to claim success at final analysis.

The efficacy boundary at the final analysis will be based on the actual number of patients and the alpha already spent at the interim analysis. If the number of patients in the final analysis deviates from the expected number of patients, the final analysis criteria will be determined so that the overall significance level across all analyses is maintained at one-sided 0.025.

4.14.2 Interim analysis for the key secondary endpoints

If the primary endpoint is met at the interim analysis, the key secondary endpoints will also be assessed following hierarchical sequence using an α-spending function according to Lan-DeMets (O'Brien-Fleming).

4.14.2.1 ORR within 3 months in all patients infused with CTL019 from US manufacturing facility

Based on the choice of α-spending functions described above, if the interim analysis is performed exactly with 50 patients and final analysis will include up to 66 patients (i.e. 50/66=75.8% information fraction), the lower bound of the 2-sided 98.0% exact CI of the ORR will need to be greater than 20% to declare statistical significance. As a result, an ORR of 18/50 = 36% is needed to claim success at interim. If the interim efficacy boundary is not crossed, 2-sided 95.6% exact CI will be used at final analysis correspondingly. As a result, an ORR of 21/66 = 32% will be needed to claim success at final analysis.

4.14.2.2 Remission with MRD negative bone marrow in patients infused with CTL019 from all manufacturing facilities

Based on the choice of α-spending functions described above, if the interim analysis is performed exactly with 50 patients and final analysis will include up to 76 patients (i.e.

50/76=65.8% information fraction), the lower bound of the 2-sided 98.9% exact CI will need to be greater than 15% to declare statistical significance. As a result, a MRD negative rate of 15/50 = 30% is needed to claim success at interim. If the interim efficacy boundary is not crossed, 2-sided 95.4% exact CI will be used at final analysis correspondingly. As a result, an ORR of 19/76 = 25% will be needed to claim success at final analysis.

4.14.2.3 Remission with MRD negative bone marrow in patients infused with CTL019 from US manufacturing facility

Based on the choice of α-spending functions described above, if the interim analysis is performed exactly with 50 patients and final analysis will include up to 66 patients (i.e. 50/66=75.8% information fraction), the lower bound of the 2-sided 98.0% exact CI of the ORR will need to be greater than 20% to declare statistical significance. As a result, an ORR of 15/50 = 30% is needed to claim success at interim. If the interim efficacy boundary is not crossed, 2-sided 95.6% exact CI will be used at final analysis correspondingly. As a result, an ORR of 17/66 = 26% will be needed to claim success at final analysis.

5 Additional analysis definitions and conventions

5.1 Response rate analyses

For the analyses of response rate (e.g, ORR), the rates will be summarized along with a 2-sided 95% exact Clopper-Pearson confidence interval. Sample code is provided below.

```
PROC FREQ data=dataset;

EXACT BINOMIAL;

TABLE outcome/binomial(p=0.2) ALPHA=0.xxx;

RUN;

/* outcome is the variable to indicate response or not, note that if the outcome is
dichotomous variable, then the proportion of outcome=0 will be calculated.*/
```

5.2 Time-to-event analyses

For time-to-event analyses (DOR, RFS, EFS and OS), the survival function will be estimated using the Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST (see examples below). Median survival will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the loglog option available within PROC LIFETEST, Kaplan-Meier estimates with 95% confidence intervals at specific time points will be summarized.

```
PROC LIFETEST data=dataset METHOD=KM conftype=loglog;

TIME survtime*censor(1);

RUN;

/* survtime represents variable containing event/censor times;

censor represents censoring variable (1=censored, 0=event); */
```

The time points can be expressed in weeks or in months depending on the time-to-event variable (e.g. overall survival might require a different scale than duration of response). If 'months' is used it should be noted that 1 month is defined as (365.25/12) =30.4375 days, which is not equal to 4 weeks.

In completing risk analysis, the cumulative incidence function (CIF) can be estimated following macro:

```
%CIF(data=dataset, out=est, time=survtime, status=status, event=1);

/* survtime represents variable containing event/censor times;

status represents status variable (0=censored, 1= event of interest, 2= competing
events); */
```

5.3 Duration of follow-up

The follow up duration (in months) for time to event endpoints (EFS and OS) is calculated as (Date of event or censoring – Date of first CTL019 infusion + 1)/30.4375.

The follow up duration (in months) for time to event endpoints (DOR, RFS and time to B cell recovery) is calculated as (Date of event or censoring – Date of onset of remission + 1)/30.4375.

Primary follow up duration (in months) will be calculated as (min(Analysis cut-off date, treatment and primary follow-up phase completion or discontinuation date) – Date of first CTL019 infusion + 1)/30.4375).

The total study follow up duration (in months) will be calculated as (min(Analysis cut-off date, Study follow-up completion or discontinuation date) – Date of first CTL019 infusion + 1)/30.4375). Here the study follow-up completion or discontinuation date will be refer to the completion/discontinuation date of the last phase (i.e. treatment and primary follow-up or secondary follow-up) the patient has entered.

5.4 Time windows

In order to summarize the patient reported outcome (PRO), growth data, PK and biomarker data over time, assessments will be time-slotted using the following time windows. These windows will be based on the study evaluation schedule and should comprise a set of days "around" the nominal visits. As a general rule, the following steps are followed to determine the cutoffs for post-baseline time windows:

- Transform all scheduled assessment time points into study days, assuming 1 month = 30.4375 days. Middle points of scheduled assessments are determined.
- The time window associated with the previous assessment ends prior to the middle point; the time window associated with the latter assessment begins after the middle point. In case the middle point is an exact study day, it will belong to the previous assessment.
- The time window of first post-baseline assessment starts with Day 2, unless otherwise indicated.

For PK, Biomarker and growth data, if more than one assessment is done within the Baseline time window, the last assessment in the baseline time window will be used. For all other time

windows, the assessment closest to the planned assessment date will be used; if two or more assessments are equidistant from the planned date, then the mean value will be used.

Table 5-1 shows the defined time windows for biomarker sample.

Table 5-1 Time windows for biomarker

Time Window	Planned visit timing (study day)	Time Window Definition (Study days)
Peripheral blood for serum cytokine analyses		
W-16 to D-1 Enrollment/Pre-Chemotherapy*	Before Study Day -1	< first day of Lymphodepleting (LD) chemotherapy
D -1 Pre-infusion**	-1	Day of LD chemo to day 1 pre infusion
D7±1d	7	Day 1 post infusion to 10
D14±3d	14	11 to 17
D21±3d	21	18 to 24
D28±4d	28	25 to 59
M3±14d	91	60 to 136
M6±14d	183	137 to 273
M12±14d	365	≥274
CTL019 Immunophenotyping; B cell; T cell (peripheral blood)		
W-16 to D-1 Enrollment/Pre-Chemotherapy *	Before Study Day -1	< first day of Lymphodepleting (LD) chemotherapy
D -1 Pre-infusion**	-1	Day of LD chemo to day 1 pre infusion
D7±1d	7	Day 1 post infusion to 10
D14±3d	14	11 to 17
D21±3d	21	18 to 24
D28±4d	28	25 to 59
M3±14d (Primary follow-up only)	91	60 to 136
M6±14d (Primary follow-up only)	183	137 to 228
M9±14d (Primary follow-up only)	274	229 to 319
M12±14d (Primary follow-up only)	365	320 to 574
M24±14d (Primary follow-up only)	731	575 to 913
M36±14d (Primary follow-up only)	1096	≥ 914
[redacted]		
W-16 to D-1 Enrollment/Pre-Chemotherapy	Before Study Day -1	< first day of Lymphodepleting (LD) chemotherapy
D28±4d	28	21 to 59
M3±14d	91	60 to 136
M6±14d	183	137 to 273
M12±14d	365	≥274
[redacted]		
CTL019 Immunophenotyping; B cell; T cell (bone marrow aspirate)		
W-16 to W-12 Screening*	Before Study Week -12	< first day of Lymphodepleting (LD) chemotherapy
D28±4d	28	21 to 59
M3±14d (recommended but not required)	91	60 to 136

M6±14d (recommended but not required)	183	≥137

Study Day 1 = start date of CTL019
* for patients who didn't receive LD chemotherapy, this window is ≤-2
**for patients who didn't receive LD chemotherapy, this window is -1 to 1 pre-infusion

As it is critical to understand the change of cytokine level during the first month of study drug and to capture the likely unscheduled assessments, a time window (Table 5-2) more frequent than protocol scheduled assessment is defined for this purpose.

Table 5-2 Time windows for serum cytokine in peripheral blood analyses within 28 days

Time Window	Time Window Definition (Study days)
W-16 to D-1 Enrollment/Pre-Chemotherapy *	< first day of Lymphodepleting (LD) chemotherapy
Pre-infusion**	Day of LD chemo to day 1 pre infusion
D4	Day 1 post infusion*** to Day 5
D7	6 to 9
D11	10 to 12
D14	13 to 15
D17	16 to 19
D21	20 to 24
D28	25 to 35

* for patients who didn't receive LD chemotherapy, this window is ≤-2
** for patients who didn't receive LD chemotherapy, this window is -1 to 1 pre infusion
*** all samples on day 1 are scheduled to be taken pre-infusion. Samples will be considered as post infusion only if time of collection is after CTL019 infusion.

Table 5-3 shows the defined time windows for CTL019 PK sample.

Table 5-3 Time windows for CTL019 PK

Time Window	Planned visit timing (Study day)	Time Window Definition (Study day)
CTL019 pharmacokinetics by q-PCR in peripheral blood		
W-16 to D-1 Enrollment/Pre-Chemotherapy	Before Study Day -1	≤ day 1 pre-infusion
D1 10 min ± 5 min post-infusion	1	Day 1 post-infusion to 2
D4±1d	4	3 to 5
D7±1d	7	6 to 9
D11±1d	11	10 to 12
D14±3d	14	13 to 17
D21±3d	21	18 to 24
D28±4d	28	25 to 59
M3±14d	91	60 to 136
M6±14d	183	137 to 228
M9±14d	274	229 to 319
M12±14d	365	320 to 456
M18±14d	548	457 to 639
M24±14d	731	640 to 913

M30±14d	913	914 to 1004
M36±14d	1096	1005 to 1187
M42±14d	1278	1188 to 1369
M48±14d	1461	1370 to 1552
M54±14d	1644	1553 to 1734
M60±14d	1826	≥ 1735
CTL019 pharmacokinetics by flow cytometry in peripheral blood		
W-16 to D-1 Enrollment/Pre-Chemotherapy	Before Study Day -1	≤ day 1 pre-infusion
D4±1d	4	Day 1 post-infusion to 5
D7±1d	7	6 to 9
D11±1d	11	10 to 12
D14±3d	14	13 to 17
D21±3d	21	18 to 24
D28±4d	28	25 to 59
M3±14d	91	60 to 136
M6±14d	183	137 to 228
M9±14d	274	229 to 319
M12±14d	365	320 to 456
M18±14d	548	457 to 639
M24±14d	731	640 to 913
M30±14d	913	914 to 1004
M36±14d	1096	1005 to 1187
M42±14d	1278	1188 to 1369
M48±14d	1461	1370 to 1552
M54±14d	1644	1553 to 1734
M60±14d	1826	≥ 1735
CTL019 pharmacokinetics by q-PCR in bone marrow aspirate		
CTL019 pharmacokinetics by flow cytometry in bone marrow aspirate		
W-16 to W-12 Screening	Before Study Week -12	≤-1
D28±4d	28	1 to 59
M3±14d (recommended but not required)	91	60 to 136
M6±14d (recommended but not required)	183	≥137
CTL019 pharmacokinetics by q-PCR in CSF		
W-16 to W-12 Screening	Before Study Week-12	≤-1
D28±4d	28	≥ 1

Table 5-4 shows the defined time windows for tocilizumab PK sample.

Table 5-4 Time windows for tocilizumab PK

Time Window	Time Window Definition
First tocilizumab dose:	
D1 (5-15 minutes post infusion)	First toci admin to <30 minutes post first toci
D1 1 hour ± 15 min post infusion	30 minutes post first toci to <12 hours post first toci
D2 ± 2 hours	12 hours post first toci to <36 hours post first toci

D3 ± 4 hours	36 hours post first toci to <96 hours post first toci
D7 ± 1d	96 hours post first toci to <192 hours post first toci
Second tocilizumab dose:	
D1 (pre-dose; second infusion)	24 hours prior to second toci admin to <second toci admin
D1(5-15 minutes post second infusion)	Second toci admin to <12 hours post second toci
D2 ± 2 hours from second infusion	12 hours post second toci to <36 hours post second toci
* Concentration on or after second tocilizumab administration will not be summarized for first tocilizumab PK.	

Table 5-5 shows the defined time windows for CTL019 PK sample.

Table 5-5 Time windows for immunogenicity

Time Window	Planned visit timing (Study day)	Time Window Definition (Study day)
W-16 to D-1 Enrollment/Pre-Chemotherapy	Before Study Day -1	≤-1
D14±3d	14	1 to 21
D28±4d	28	22 to 59
M3±14d	91	60 to 136
M6±14d	183	137 to 273
M12±14d	365	274 to 574
M24±14d	731	575 to 913
M36±14d	1096	≥ 914
Study Day 1 = start date of CTL019		

Table 5-6 shows the defined time windows for growth data and Tanner staging.

Table 5-6 Time windows for growth data and Tanner staging

Time Window	Planned visit timing (Study day)	Time Window Definition (Study day)
Height and Tanner Stage		
Baseline	Before Study Week -12	≤1
M6±14d	183	>1 to 273
M12±14d	365	274 to 456
M18±14d	548	457 to 639
M24±14d	731	640 to 913
M30±14d	913	914 to 1004
M36±14d	1096	1005 to 1187
M42±14d	1278	1188 to 1369
M48±14d	1461	1370 to 1552
M54±14d	1644	1553 to 1734
M60±14d	1826	≥ 1735
Weight		
Baseline	Before Study Week -12	≤-3
D-1±1d	-1	-2 to -1
D28±4d	28	21 to 59
M3±14d	91	60 to 136
M6±14d	183	137 to 228
M9±14d	274	229 to 319

M12±14d	365	320 to 456
M18±14d	548	457 to 639
M24±14d	731	640 to 913
M30±14d	913	914 to 1004
M36±14d	1096	1005 to 1187
M42±14d	1278	1188 to 1369
M48±14d	1461	1370 to 1552
M54±14d	1644	1553 to 1734
M60±14d	1826	≥ 1735

Study Day 1 = start date of CTL019

Table 5-7 shows the defined time windows for patient reported outcome.

For PRO, if more than one assessment is done within the Baseline time window, the assessment closest to and before the first day of study treatment will be used. For all other time windows, if two assessments are obtained with the same time difference compared to the scheduled visit day, the assessment obtained prior to the scheduled visit will be considered.

Table 5-7 Time windows for patient reported outcome

Time Window	Planned visit timing (study day)	Time Window Definition (Study days)
W-16 to D-1	Before Study Day -1	Last one before first day of study treatment
D28±4d	28	21 to 59
M3±14d	91	60 to 136
M6±14d	183	137 to 228
M9±14d	274	229 to 319
M12±14d	365	320 to 456
M18±14d	548	457 to 639
M24±14d	731	640 to 913
M36±14d	1096	914 to 1278
M48±14d	1461	1279 to 1643
M60±14d	1826	≥ 1644

Study Day 1 = start date of CTL019 infusion

5.5 Handling of missing or partial dates

Missing or partial date imputation will be conducted according to the logic described in this section. The imputed dates will be used for the calculation of duration of events. However, in the listings only the original reported dates will be listed.

5.5.1 AE date imputation

Date imputation is the creation of a new, complete date from a partial one according to an agreed and acceptable algorithm. Missing date for AE will be handled according to rules specified below. A partial date is simply an incomplete date e.g. DDOCT2001: the days are missing from this DDMMMYYYY date.

Partial AE start dates, if left partial, would ultimately mean the following:

It would not be possible to place the AE in time.

Therefore the treatment/dosage at the time of the event would be unknown.

Therefore the event could not be reported/summarized appropriately – if at all.

Therefore it is important to perform date imputation to ensure that as many data events are represented as correctly as possible. Of course partial and/or missing dates should *also* be caught as edit checks and passed back to the investigator for resolution.

AE start date will be imputed as follows:

The following Table 5-8 explains the abbreviations used.

Table 5-8 AE/treatment date abbreviations

	Day	Month	Year
Partial Adverse Event Start Date	<not used>	AEM	AEY
Treatment Start Date (TRTSTD)	<not used>	TRTM	TRTY

The following matrix Table 5-9 describes the possible combinations and their associated imputations. In the table body the upper text indicates the imputation and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 5-9 AE partial date imputation algorithm

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	NC Uncertain	NC Uncertain	NC Uncertain	NC Uncertain
AEY < TRTY	(D) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD
AEY = TRTY	(B) Uncertain	(C) Before TRTSTD	(B) Uncertain	(A) After TRTSTD
AEY > TRTY	(E) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD

The following Table 5-10 is the legend to the above table.

Table 5-10 AE/treatment date relationship and imputation legend

Relationship	
Before TRTSTD	Indicates AE start date prior to Treatment Start Date
After TRTSTD	Indicates AE start date after Treatment Start Date
Uncertain	Insufficient to determine the relationship of AE start date to Treatment Start Date
Imputation Calculation	
NC / Blank	No convention/imputation
(A)	01MONYYYY
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

The following Table 5-11 gives a few examples.

Table 5-11 AE imputation example scenarios

Partial AE start date	Treatment start date	Relationship	Imputation Calculation	Imputed Date
12mmyyyy	20OCT2001	Uncertain	NC	<blank>
ddmmm2000	20OCT2001	Before	(D)	01JUL2000
ddmmm2002	20OCT2001	After	(E)	01JAN2002
ddmmm2001	20OCT2001	Uncertain	(B)	21OCT2001
ddSEP2001	20OCT2001	Before	(C)	15SEP2001
ddOCT2001	20OCT2001	Uncertain	(B)	21OCT2001
ddNOV2001	20OCT2001	After	(A)	01NOV2001

Note, it may happen that the imputed AE start is after AE end date, in that case, imputed AE start=AE end date.

There **will be no** attempt to impute the following:

- **Missing** AE start dates
- AE start dates **missing the year**

Partial AE end date will be imputed as follows:

- Imputed date = min (date of death if applicable, last day of the month), if day is missing;
- Imputed date = min (date of death if applicable, 31DEC), if month and day are missing.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

Missing AE end date or AE end date after data cutoff will be imputed as follows:
All events with start date before or on the cut-off date, and with end date missing or after the cut-off date will have the end date imputed as the minimum of the cut-off date, end of study evaluation (i.e. completion of the last phase of the study) or date of death (if applicable). For these events, the imputed end date will not appear in the listings, instead, they will be reported as "continuing".

5.5.2 Concomitant medication date imputation

The imputation of the start date of concomitant medication will follow the same conventions as for AE date. Partial concomitant medication end dates will not be imputed.

5.5.3 Incomplete date for anti-neoplastic therapies

Prior therapies

Start date:

The same rule which is applied to the imputation of AE/concomitant medication start date will be used with the exception that for scenario (B) will be replaced to be 'start date of study treatment -1'.

End date:

Imputed date = min (start date of study treatment, last day of the month), if day is missing;

Imputed date = min (start date of study treatment, 31DEC), if month and day are missing.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

Post therapies

Start date:

Imputed date = max (last date of study treatment + 1, first day of the month), if day is missing;

Imputed date = max (last date of study treatment + 1, 01JAN), if day and month are missing.

End date: No imputation.

5.5.4 Incomplete assessment dates for tumor assessment

All investigation dates (e.g. peripheral blood, bone marrow) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date

is calculated as the latest of all investigation dates (e.g. peripheral blood, bone marrow) if the overall disease response at that assessment is CR/CRi/UNK. Otherwise, if overall lesion response is relapsed disease or no response, the assessment date is calculated as the earliest date of all investigation dates at that evaluation number that reveals a relapse/no response. If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.

5.5.5 Incomplete date for relapse or last known date subject in remission

The "Remission/Relapse Information" CRF will be used to track the relapse status for those patients who enter the secondary follow up phase while in remission.

If the day or month of date of relapse or last known date subject in remission is missing, it will be imputed to the minimal of date of assessment and the following:

- Missing day: 15th day of the month and year
- Missing day and month: July 1st of the year

5.5.6 Incomplete date for death or last known date subject alive

If the day or month of death is missing from the death CRF, death will be imputed to the maximum of the full (non-imputed) last contact date (Section 3.1.8) and the following:

- Missing day: 15th day of the month and year of death
- Missing day and month: July 1st of the year of death

If the day or month of last known date subject alive is missing in the survival CRF, it will be first imputed with the following:

- Missing day: minimum of the date of assessment and 15th day of the month and year of last known date subject alive
- Missing day and month: minimum of the date of assessment and July 1st of the year of last known date subject alive

Then the above imputed last know date subject alive will be used to calculate the last contact date as defined in Section 3.1.8.

5.5.7 Incomplete date for initial diagnosis, first relapse and most recent relapse

If the day or month of initial diagnosis, first relapse or most recent relapse is missing, the date of initial diagnosis will be imputed to the minimum of the informed consent date -1 and the following:

- Missing day: 15th day of the month and year
- Missing day and month: July 1st of the year

5.5.8 Date of hospitalization imputation

Missing hospitalization end date or end date after data cutoff will be imputed following the same conventions as for AE end date imputation.

5.6 Determination of missing scheduled disease assessments

For some time-to-event endpoints (i.e. DOR, RFS, EFS), classification of censoring or event can depend on the number of missing scheduled disease assessments.

The protocol defined schedule of disease assessments is every month for the first 6 months, every 3 months thereafter until Month 24, and every 6 months thereafter until Month 60. Each assessment is expected to be performed at the scheduled time point plus or minus 2 weeks in general, i.e. the window is 4 weeks or 1 month.

An event is considered as after 2 or more missing scheduled disease assessments if the distance between the last adequate non-relapse assessment and the event is larger than the threshold, defined as two times the protocol specified interval between the disease assessments plus the protocol allowed window around the assessments.

More specifically, an event is considered as having occurred after 2 or more missing scheduled disease assessments if the distance between the last adequate non-relapse assessment and the event is:

- >91 days (i.e. 1+1+1 months), if the last adequate non-relapse assessment occurs on or before Day 136 (i.e. middle point of Month 4 and Month 5)
- >152 days (i.e. 1+3+1 months), if the last adequate non-relapse assessment occurs after Day 136 and on or before Day 167 (i.e. middle point of Month 5 and Month 6)
- >213 days (i.e. 3+3+1 months), if the last adequate non-relapse assessment occurs after Day 167 and or on before Day 593 (i.e. middle point of Month 18 and Month 21)
- >304 days (i.e. 3+6+1 months), if the last adequate non-relapse assessment occurs after Day 593 and on or before Day 684 (i.e. middle point of Month 21 and Month 24)
- >395 days (i.e. 6+6+1 months), if the last adequate non-relapse assessment occurs after Day 684

5.7 EFS category

Patients will be categorized into EFS categories for exploratory analysis (e.g. EFS category vs manufactured product characteristics, etc.):

- EFS ≥ 6 (or 3) months: if patient achieved remission, and EFS event or censoring day ≥ 6 (or 3) months
- EFS event < 6 (or 3) months: if patient achieved remission, and EFS event day < 6 (or 3) months.
- EFS censor < 6 (or 3) months: if patient achieved remission, and EFS censor day < 6 (or 3) months
- Treatment failure: if patient is treatment failure
- Other: if patient does not satisfy any of above (i.e. pending patients who have not achieved CR nor have been classified as treatment failure; will NOT be included in the analysis)

Here EFS ≥ 6 months is determined by whether EFS (in days) is ≥ 167 days (i.e. 5.5 months). Similarly, EFS ≥ 3 months is determined by whether EFS (in days) is ≥ 76 days (i.e. 2.5 months).

5.8 CNS disease history search

CNS disease history is defined by the following MedDRA terms as collected in medical history:

- Neurological disorders congenital (HLGT)
- Congenital and peripartum neurological conditions (HLGT)
- Central nervous system haemorrhanges and cerebrovascular accidents (HLT)
- Noninfectious encephalopathy/delirium (SMQ) (broad)

6 References

Baumgartner RN, Roche AF, Himes (1986). Incremental growth tables: supplementary to previously published charts. American Journal of Clinical Nutrition, 43, 711-722.

CHMP (2010) Appendix 2 to the Guidance on the evaluation of anticancer medicinal products in man (CPMP/EWP/205/95 Rev. 3) on confirmatory studies in haematological malignancies

Fenichel P (2012). Delayed puberty. Endocr Dev, 22, 138-59.

Harrison CJ, Haas O, Harbott J, et al. (2010) Detection of prognostically relevant genetic abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia: recommendations from the Biology and Diagnosis Committee of the International Berlin-Frankfürt-Münster study group. Brit J Hematol; 151(2):132-142.

Jeha S, Gaynon PS, Razzouk BI, et al. (2006) Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. J Clin Oncol, 24:1917–23

Kim H (2007) Cumulative Incidence in Competing Risks Data and Competing Risks Regression Analysis. Clinical Cancer Research 2007;13:559-565

National Comprehensive Cancer Network (NCCN) Guidelines (NCCN, 2013 vl), Acute Lymphoblastic Leukemia

O'Brien S, Schiller G, Lister J, et al. (2013) High-Dose Vincristine Sulfate Liposome Injection for Advanced, Relapsed, and Refractory Adult Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia 34, 676-83

Tanner JM, Goldstein H, Whitehouse RH (1970). Standards for children's height at ages 2-9 years allowing for height of parents. Archives of Disease in Childhood, 45, 755-762.

Topp M, Gokbuget N, Stein A, et al. (2015) Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol; 16: 57-66.

van der Veer A, Waanders E, Pieters R, et al. (2013) Independent prognostic value of *BCR-ABL1-like* signature and *IKZF1* deletion, but not high *CRLF2* expression, in children with B-cell precursor ALL. Blood; 122(15):2622-2629.

7 Appendix

CDC Growth Charts (http://www.cdc.gov/growthcharts/percentile_data_files.htm) for height (STATAGE) and weight (WTAGE) for children older than 2 years.


statatage.csv


wtage.csv